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INFECTIVE RETICULO-ENDOTHELIOSIS CHIEFLY LOCALIZED IN LUNGS, BONE MARROW AND THYMUS

BY

S. VAN CREVELD, M.D., AND F. H. TER POORTEN, M.D.

(From the Propaedeutic Clinic and the Pathological Laboratory, University of Amsterdam.)

Recently a number of articles have been published on a morbid condition observed especially in young children, in which after death proliferation of the reticulo-endothelial system has been found. This proliferation affected not only the reticulo-endothelium as such, but also groups of cells, such as the histiocytes of Aschoff and the Kupffer cells, which may be looked upon as belonging to this system because they show some of its most prominent characteristics, e.g. phagocytosis and ability to store substances. Depending upon whether it is considered that such proliferation arises in the reticulo-endothelium, or in the mesenchymatous cells in connective tissue and round the blood vessels, the morbid process is known variously as reticulosis, reticulo-endotheliosis and histiocytosis.

Of the reticulo-endotheliosis group, which histologically may show great variety in localization as well as in intensity, some sub-groups have already been separated: a. those where a known aetiological factor can be affirmed (tuberculosis, typhoid); and b. those which show characteristic localization and where the proliferated cells have accumulated easily recognized substances. This is the case in the lipoidoses showing a deposit of kerasine in Gaucher's disease, of phosphatides in the disease of Niemann-Pick, of cholesterol and cholesterol-esters in the xanthomatoses. Of the xanthomatoses one has been set apart, namely, the disease of Schüller-Christian, which is caused by the localization of the deposits in the skull and pituitary and characterized by membranous defects in the skull (map-skull), with or without exophthalmus and diabetes insipidus. It may be questioned as to how far a sharp separation of the lipoidoses, especially xanthomatosis, from other proliferations of the reticulo-endothelial system is fully justified, in view of the fact that the deposit of cholesterol and cholesterol-esters with the appearance of typical so-called foam-cells may disappear at a certain stage of the disease[1, 2], whereas in other types of reticulo-endothelial proliferation they may appear secondarily.

Putting aside the two groups mentioned above, there still remain a number of cases the classification of which gives rise to difficulty. The clinical picture as well as the localization of the histological changes differ. This point will be discussed later, after the description of the patient under our observation, whose malady, in our opinion, belongs to this group of reticulo-endothelioses.

Case record.

A girl of four-and-a-half months was admitted to the Infants Department of the Propaedeutic Clinic on May 3, 1934. She was the tenth child of healthy parents; the other children were all well. The child was born normally at term and during the first months of life was well, except for a purulent discharge from the right ear from the fourth week of life. The otitis still existed when the child came into the hospital. The patient was brought because ten days before the mother had noticed that the right arm was moved with pain and difficulty. Four days later she observed the same symptoms in the right leg. The child was not ill, had no elevation of temperature and did not vomit. At first an injury was thought to be the cause of the condition, but later the possibility of poliomyelitis was considered. A skiagram of the right arm however revealed a cystic process in the proximal part of the right humerus. At this stage the infant was admitted to the department. The child was quiet, except for a slight cough. The skull was slightly bossed; the anterior fontanelle had a diameter of about half an inch. Just above the left parietal prominence there was a small soft area with thickened borders. The face was swollen. The eyes showed no abnormality, there was no exophthalmus and the sclerae were normal. The mucous membranes of mouth and throat were pale. In the neck on both sides some small lymph nodes were palpable. There was a slight rachitic rosary; on the chest-wall were some small furuncles. The liver edge was felt one finger-breadth below the costal margin; the spleen was just palpable. The right arm and leg were not quite so freely movable as the left but there was no tenderness. The reflexes were normal. In axillae and groins some small glands could be felt and in the lower middle part of the back a few small nodules were palpable, situated probably in the subcutaneous tissue. Over both lungs many coarse bronchitic râles could be heard. The von Pirquet and Mantoux tests were negative. The urine was normal, there being no Bence-Jones proteose or microscopical abnormality. The Wassermann reaction was negative. The calcium-content of the serum was normal, the inorganic phosphate-content of the blood was not increased, non-protein nitrogen was normal, and the cholesterol content of the blood was slightly increased (227 mgm. per cent.). The blood sugar content fasting was normal; a blood sugar curve after ingestion of glucose was prolonged without an abnormal rise. Bacteriological examination of stools and urine was negative. The results of the blood counts on different dates are summarized in table 1. From this table it appears that in the beginning there was a

TABLE 1.—BLOOD PICTURE ON DIFFERENT DATES.

Date	Haemoglobin (Sahli) per cent.	Red cells per c.mm.	White cells per c.mm.	Platelets (Fonio) per c.mm.	Differential leucocyte count per cent. of white cells.							
					Myelocytes	Band-formed leucocytes	Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Monocytes	Plasma cells
29.IV.34	58	4,600,000	10,200	—	—	2½	49½	—	—	36½	11½	—
4.V. ...	73	5,200,000	10,600	not decreased	½	5½	51	3	—	32	8	—
15.V. ...	68	4,720,000	11,100	377,600	—	8½	40½	—	—	42½	7	1½
17.VI. ...	57	4,740,000	8,200	—	½	6½	31	½	½	58	3	—

slight leucocytosis with a moderate monocytosis; there was no definite anaemia. The temperature during the first weeks was not raised. A detailed x-ray investigation of the skeleton showed that in addition to the cystic condition in the proximal part of the humerus (fig. 1) there existed some membranous defects in the skull (fig. 2). A control skiagram demonstrated

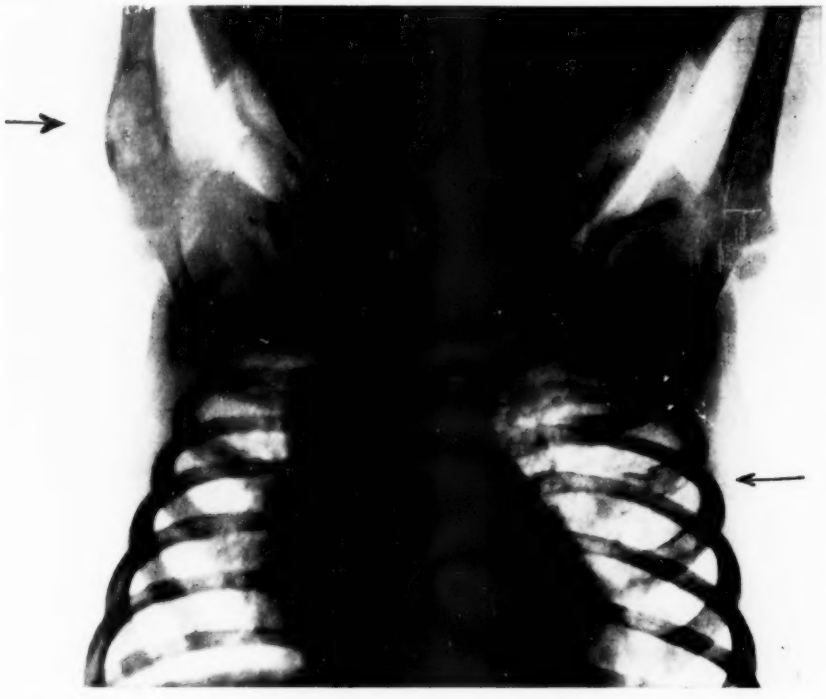

FIG. 1.—Cystic focus in the proximal part of the right humerus and in the left third rib.

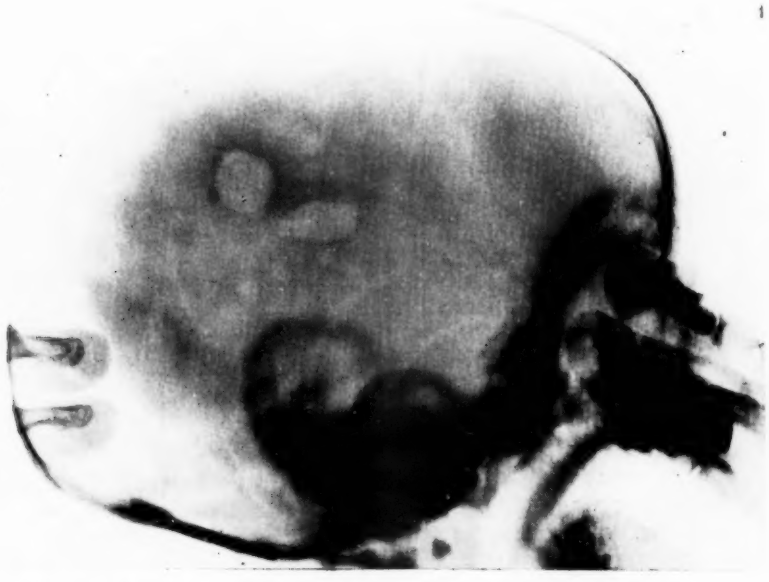

FIG. 2.—Membranous defects in the skull (condition on 4.V.1934).

that one of these defects corresponded with the palpable defect. It further appeared that there was a cystic rarefaction in the left third rib (fig. 1) and some in the distal part of the right femur (fig. 3) and the left tibia. The x-ray of the lungs showed slight consolidation at the hila and a few opacities in both lungs. The sella turcica was normal.

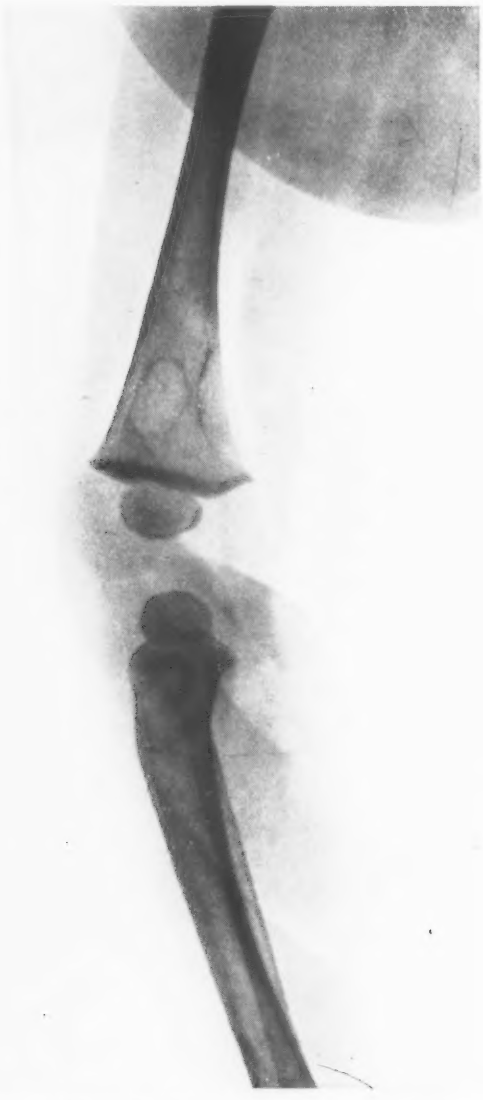

FIG. 3.—Cystic foci in the distal part of the right femur.

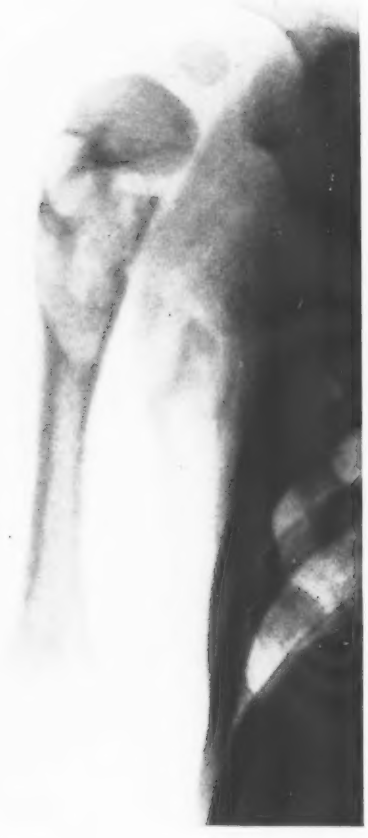

FIG. 4.—Extension of the focus in the right humerus.

During the stay in the hospital the discharge from both ears varied; on two occasions paracentesis of both drums had to be performed. A swelling of the right cheek was noticed for some days. Behind both ears some small nodules were palpable; whether or no they were fixed to the underlying bone remained uncertain. The body temperature was almost constantly raised after the first two weeks.

While under obervation the number of areas of softening in the skull increased, but still more did the number of defects visible in the skiagram of the skull; a real map-skull developed. The defect in the humerus enlarged and the cortex of the bone was much more involved (fig. 4). At a later stage active and passive movements of the arms and legs appeared to be fairly normal. The skiagram of the lungs showed more abnormalities; dyspnoea increased, but on auscultation only coarse râles could be heard. The bodily condition remained normal, the face became somewhat swollen (fig. 5), the spleen and liver, especially the liver, felt larger.

On May 18 the nodule palpable behind the left ear was aspirated. Some giant cells and some epitheloid cells were found (fig. 6), but no tubercle bacilli were seen. Certainty about the diagnosis could not be obtained in this way. This will be referred to later.

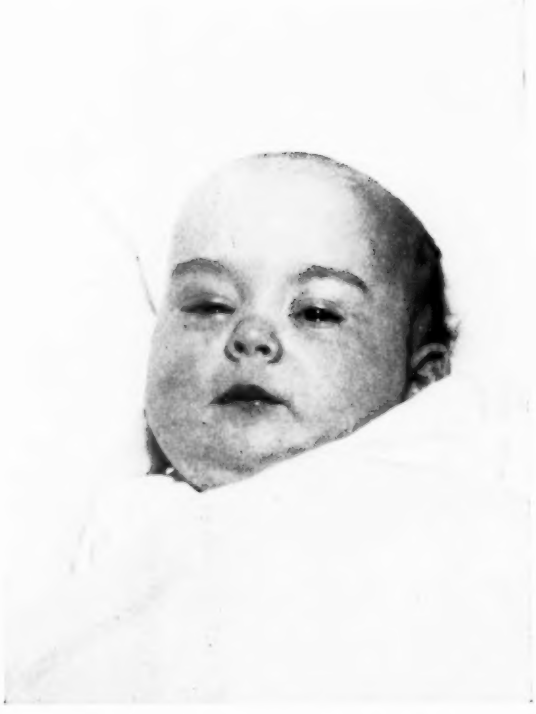

FIG. 5.—Photograph of child (16.V.1934).

FIG. 6.—Giant cells and epitheloid cells in the puncture-fluid from a nodule behind the ear.

The nodules in the back provided a further possible clue to the diagnosis. They could be felt about six cm. above the anal cleft. At the end of May they had slightly increased in size, were probably three in number, of fairly firm consistency, lying under the skin but attached to it. One of the nodules was removed under local anaesthesia; microscopical investigation showed that this was of the nature of an adiponecrosis subcutanea neonatorum[3]. The relation of the fat-necrosis to the rest of the clinical picture, especially to the bone-defects, remained obscure to us.

On June 17 the general condition was still the same, temperature high, colour pale although the haemoglobin content was still 57 per cent. A skiagram of the lungs, on June 14, had shown that on both sides there were many small bronchopneumonic infiltrations and particularly the picture of

the right lung seemed to point to the formation of small cavities (honeycomb-structure). On June 18 the child died suddenly. Two-and-a-half hours after death the thorax and skull were again x-rayed; in the right side of the thorax a pneumothorax was visible (fig. 7), and the skiagram of the skull showed that the number of defects had increased considerably (fig. 8).

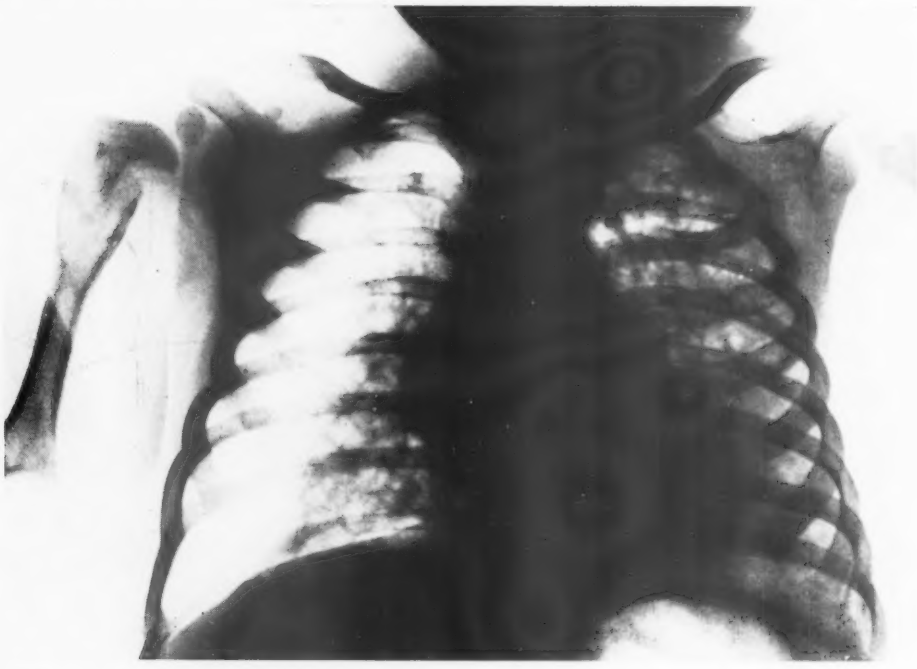

FIG. 7.—Pneumothorax in the right side of the thorax. Honeycomb structure of lungs well marked. The cortex of right humerus is still more involved.

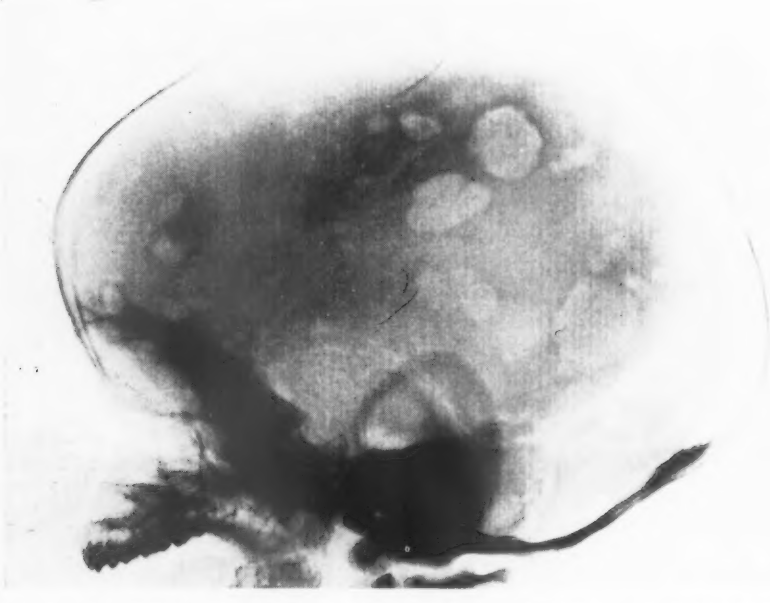

FIG. 8.—Increase of the number of defects in the skull (map-skull) (18.VI.1934).

As regards the bacteriological investigation, in the fasting stomach content no tubercle bacilli were found, the guinea-pig tests with this fluid remained negative, as well as blood culture, and so also did a further bacteriological investigation of stools and urine. The cholesterol content of the blood two days before death had increased to 596 mgm. per cent. with a normal relation between free cholesterol and cholesterol-esters; the lecithin content of the blood was normal, but lowered with regard to the cholesterol.

Short summary of the clinical data.—Otitis media purulenta duplex, osteitis cystica generalisata with map-skull, rickets, micro-polyadenia, hepatomegaly, splenomegaly, broncho-pneumonia, bronchiectasis (?), adipo-necrosis subcutanea neonatorum and pneumothorax as cause of death.

Differential diagnosis.

In order to explain the most prominent features, the multiple bone defects, the following possibilities have to be considered.

1. Osteitis fibrosa generalisata. This disease was regarded as improbable in view of the normal calcium-content of the serum, the absence of a palpable parathyroid tumour, the simultaneous existence of a visceral affection, and the different appearance of the bone defects, especially of those in the skull. Further, osteitis fibrosa is a rare disease in childhood.

2. A malignant tumour (sarcoma metastases or perhaps metastases of a neuroblastoma, or perhaps chloroma). The good general condition until death, the absence of orbital metastases and of any indication of the existence of a malignant tumour obtained in the investigation of the aspirated nodule, were the principal arguments against this possibility.

3. Osteitis tuberculosa cystica with visceral tuberculosis. In itself osteitis tuberculosis cystica is a rare affection; multiple defects in the skull have been described in it, usually associated with cold abscesses in the skull over the defects. The abscesses were absent here and there was no evidence of tuberculous infection.

4. Myelomatosis. Bence-Jones proteose was absent from the urine. In the rare cases of myelomatosis observed at this age, the x-ray appearance, especially of the skull, was different from that in our patient, and the disease progressed here too rapidly for this condition.

5. Xanthomatosis generalisata. In this patient there might be xanthomatosis ossium generalisata as well with visceral xanthomatosis. The combination of the affected organs, the beginning of the disease after a purulent otitis media has also been observed in other cases; the good general condition, the steady increase in the cholesterol-content of the blood all seemed to be in favour of the diagnosis of xanthomatosis. There have been described in the literature cases of that particular form of xanthomatosis which bears the name of Schüller-Christian's disease in which of the well-known triad of symptoms only one or two were present[4]. With the varying

localization of the process this can easily be understood. As regards the rapid extension of the membranous defects in the skull in the present case, this in itself did not exclude the diagnosis of xanthomatosis for rapid extension as well as rapid disappearance are observed in this disease. The fact that no foam-cells were found on aspiration also was no absolute argument against the diagnosis of xanthomatosis. The possibility existed that this was one of those cases, reported recently, in which foam-cells, present at the beginning, had disappeared at a later stage or in which the deposit of cholesterol and cholesterol-esters had not become generalized. In view of all these facts it appeared that this was a case of xanthomatosis generalisata.

To correspond with this diagnosis it was expected to find at autopsy a macroscopical and microscopical picture which is regarded as being typical of generalized xanthomatosis, i.e., an extensive hyperplasia of part of the reticulo-endothelial system in the bone marrow, liver, spleen, lymph nodes, perhaps also in the lungs, with accumulation of cholesterol and cholesterol-esters (Rowland[5]). As regards the lung condition which had given rise to a pneumothorax, it might either be due to xanthomatosis of the lungs, or with a process independent of xanthomatosis and related to cavity formation.

Autopsy report.

The body was that of a normally-built infant, 67 cm. in length, weight 6·5 kgm., fairly well-nourished. In the vertex of the skull several soft areas were felt, some of which had a diameter of more than 1 cm. Signs of mild rickets were present.

A pneumothorax was present on the right side with slight fibrinous pleurisy. The lungs on the surface as well as on the cut surface (fig. 9 (a) and (b)) were crowded with greyish-yellow opaque nodules, which when larger than 1 mm. show a central cavity. These cavities sometimes were as large as a pea but even then their wall was formed by a small layer of the same firm greyish-yellow mass, and not by the lung tissue as in alveolar emphysema. Repeatedly an open communication was seen between the cavities and a bronchus.

The pneumothorax appeared to have been caused by the bursting of two of these vesicles at the base of the right lung.

In the position of the thymus there was a mass of firm consistency, 5·5 cm. in length, 2·5 cm. broad and 3 cm. thick, of which the rather smooth anterior surface was connected with the front wall of the thorax by loose connective tissue. The rest of this mass was adherent to trachea, pericardium and lungs, especially on the right side. The cut surface of this mass had an appearance that did not at all resemble the thymus or lymph nodes. It was a somewhat granular, brittle, cut surface, faint greyish-yellow, with several irregularly formed, opaque yellow spots and some small slightly sunken fibrous stripes, which gave the whole mass a lobular marking. The trachea and bronchi were not narrowed.

There was no pericardial effusion and the heart was normal.

The lymph nodes were all soft and swollen. In the right axilla some nodes showed on section a single greyish-yellow spot of the same appearance as the lung nodules; all other lymph nodes were greyish-pink and free from tuberculosis. The lymphoid tissue of the intestine was slightly swollen, but not ulcerated. The spleen was soft and weighed 45 gm. In the liver (320 gm.) there were some greyish-yellow nodules, at most 1·5 mm. large.

The other organs of neck, thorax and abdomen were normal. Examination of the skull was not allowed.

In the bone marrow of the sternum there were greyish-yellow areas which did not otherwise differ distinctly in structure and consistency from the surrounding red bone marrow. In the upper part of the right humerus the bone marrow was changed from 1 cm. below the epiphyseal line for a length of 2·5 cm. into a somewhat soft, brittle, opaque greyish-yellow mass, in which were several rather more yellow areas. This mass was sharply

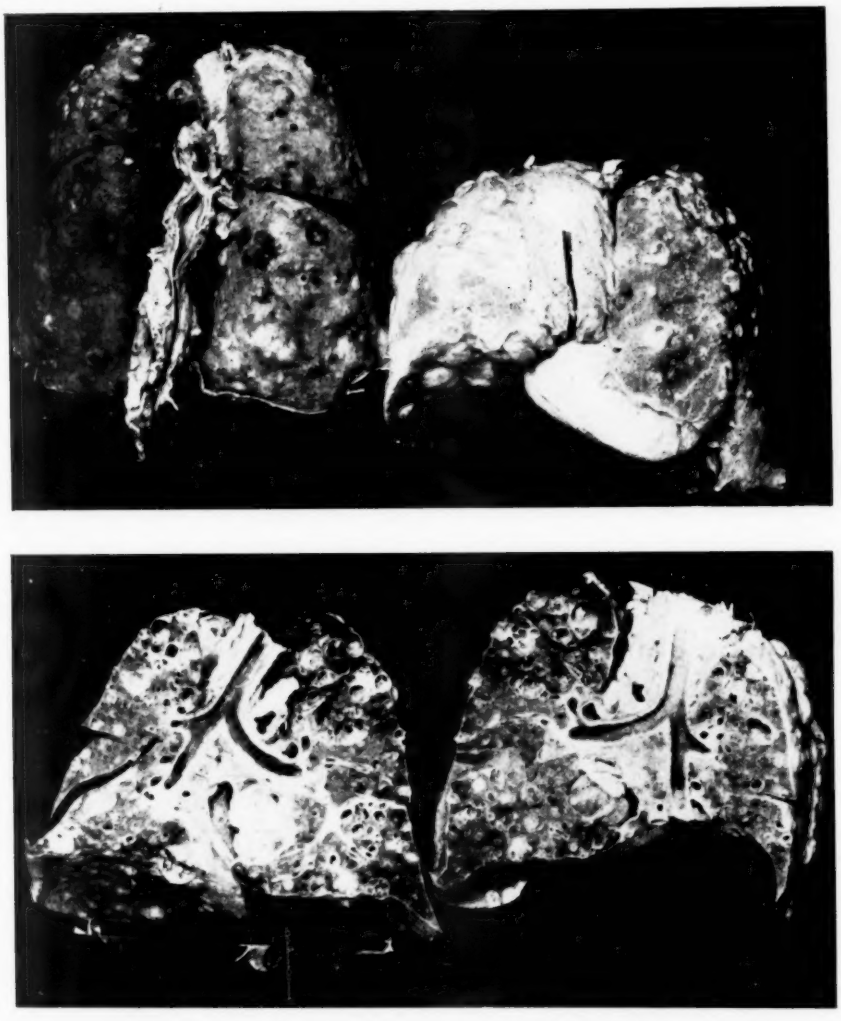

FIG. 9.—(a and b). Surface and cut surface of the lungs.

defined from the red bone marrow and, over it, the cortex was irregularly thinned and bent outwards. In the anterior end of the left third rib the bone marrow was altered for a length of several cm. into a light grey or light yellow, soft, often mucous mass, which here and there was directly adjacent to the periosteum.

The autopsy findings were not easy to interpret satisfactorily. The nodular character of the affection resembled tuberculosis, but there was no evidence of a primary lung or intestinal focus. On the other hand, the general impression was that the thymus formed the centre of the pathological

process, so that the possibility of a malignant tumour of thymus or mediastinal lymph nodes with visible metastases in lungs, lymph nodes, bone marrow and liver was considered. The histological examination brought the solution of the problem.

Microscopic examination. THYMUS. Of the thymus tissue only little was left. Only cells with a large amount of protoplasm were seen and this was poorly stained by eosin, so-called pale cells, one to ten times as large as a leucocyte, with one or more nuclei, which in size and structure resembled the endothelial nuclei. The cells were surrounded by fine fibres of reticulum which now and then were thickened to broad waving bundles staining red by van Gieson's method, and everywhere connected to the wall of the often-numerous vessels. Especially the larger polynuclear cells which seldom resembled the type of Langhans, often showed active phagocytosis (destruction products, lymphocytes, granulocytes, erythrocytes). The tissue which had taken the place of the thymus showed focal necrosis. As remnants of the thymus or of the lymph nodes next to it, were to be seen here and there accumulations of lymphocytes, in the outer layers of which often lay a large number of large pale cells showing phagocytosis. Also as remnants of the thymus tissue were interpreted the rather numerous fields, consisting of necrotic nuclei as large as a lymphocyte, and which are surrounded by a thin layer of flat epithelial-like cells, partly horny without intercellular material. The whole could thus be regarded as a Hassall's corpuscle, enlarged to ten to twenty times the original size by invasion of necrotizing lymphocytes (fig. 10). They closely resembled Dubois' abscesses.

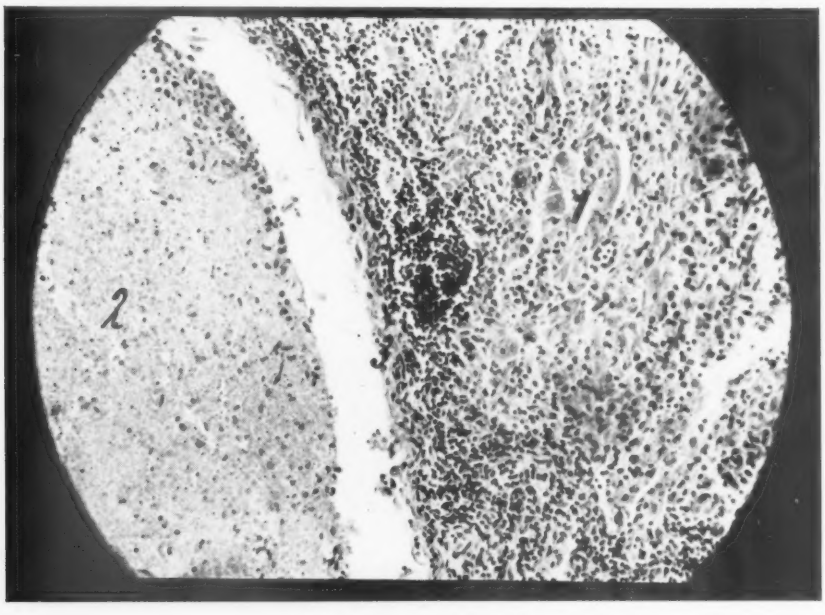

FIG. 10.—Thymus.

1. Proliferated reticular cells (pale cells) among the lymphoid thymus tissue.
2. Necrotic centre of a greatly enlarged Hassall's corpuscle.
3. Exterior horny epithelial layer of a Hassall's corpuscle.

LUNGS. The nodules in the lungs consisted of the same cells as those in the thymus; the smallest were surrounded by a broad infiltrate of lymphocytes. Some nodules were lying in the middle of the lung tissue: the proliferated cells were to be seen in the alveolar septa which had grown

much broader by this proliferation, whereas the alveoli themselves were coated with a more or less cubical epithelium, such as is seen in chronic pneumonia (fig. 11). Most of the nodules, however, arose from the walls of the vessels and especially of the bronchi (fig. 12), by which process the latter were to a great extent destroyed and partly blocked.

By means of the well-known piston-action it is easy to explain from these findings the formation of the cavities, which macroscopically resembled alveolar emphysema. The new tissue not only showed an inclination to necrosis but also it seemed to be brittle. Microscopically the walls of the cavities were not formed by lung tissue, but by proliferated cells, in which sometimes remnants of bronchial epithelium could be seen.

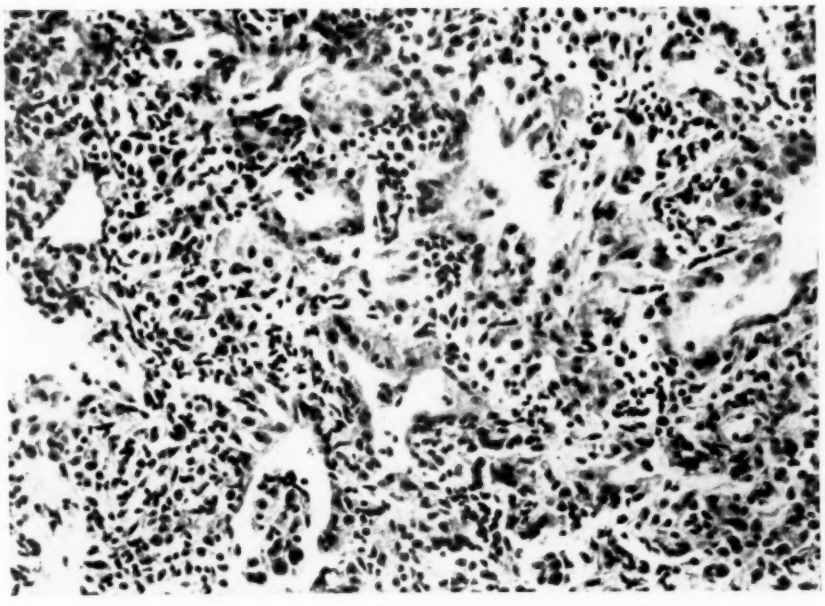

FIG. 11.—Area of cellular proliferation in the middle of the lung tissue. The proliferated cells are found in the broadened alveolar septa. The alveoli are coated with cubical epithelium.

LYMPH NODES. Everywhere there was so-called ' sinus catarrh.' Furthermore, here and there cellular proliferation at the border or in the centre of the follicles could be seen. In one axillary gland there was a large nodular proliferation in the wall of the outer sinus.

SPLEEN. This organ contained a good deal of blood. Spreading cellular proliferation issued either from the walls of the vessels, which they surrounded like a cloak, or of the red pulp, in which case they penetrated the follicles from the periphery (fig. 13).

LIVER. There were small areas of cellular proliferations, with extensive infiltration of lymphocytes round the bile ducts. The larger proliferations showed distinct connections with the peri-portal connective tissue.

BONE MARROW (STERNUM). The same cellular proliferation was seen with necrosis, of which the fine thread-like reticulum is connected to the wall of the vessels. Decrease of the myeloid elements was present and also bone destruction.

OTHER ORGANS. The thyroid gland, heart muscle, suprarenal glands, kidneys, pancreas, lymphoid tissue of the gastro-intestinal tract, and some voluntary muscles showed no cellular proliferation on microscopic examination.

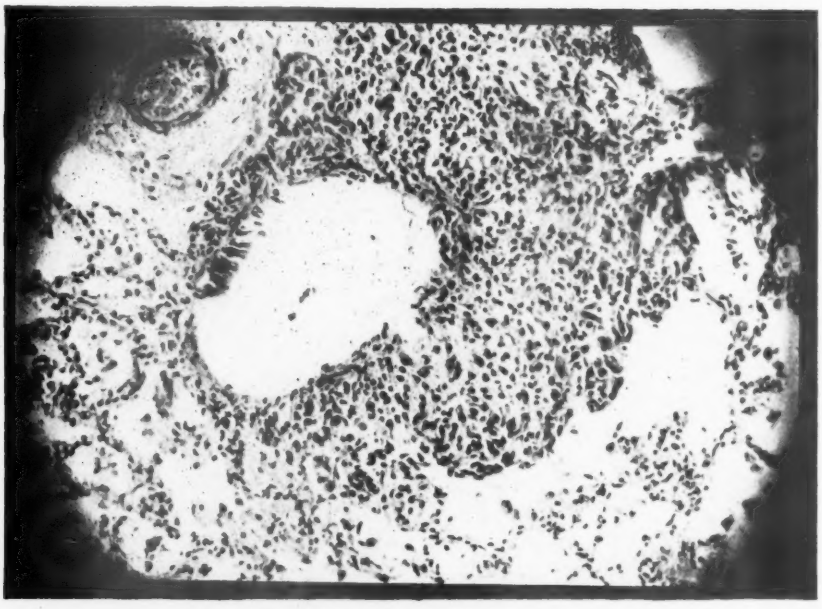

FIG. 12.—Cellular proliferation in the lung issuing from the bronchial wall. The bronchial wall can be recognized by the remains of cylindric epithelium and by its situation next to an artery.

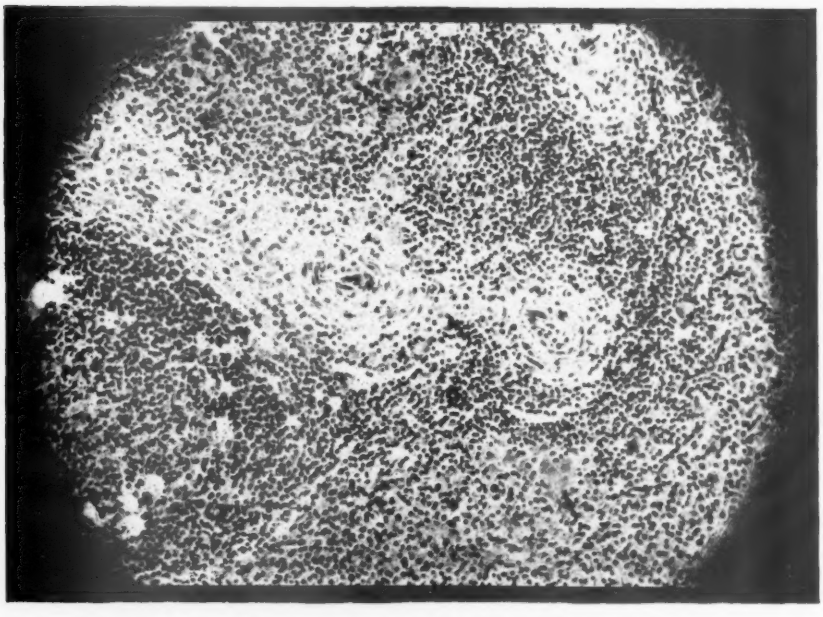

FIG. 13.—Spleen. Peri-adventitial cellular proliferation.

Bacteriological examination for tubercle bacilli, spirochaeta pallida and that of Gram-stained sections was everywhere negative. On histological examination of the proliferated cells accumulations of fat or of lipoids could nowhere be found.

Discussion of pathological findings.

The results of the autopsy and of the microscopic examination justify the diagnosis of an unusual localization of an affection which in recent years has been described several times: a so-called reticulo-endotheliosis. The provisional diagnosis made during life was confirmed in so far as a reticulo-endotheliosis was indeed found, but not that form which is known as xanthomatosis. Typical foam-cell proliferation was not found in any organ, and certainly not in the bone marrow, and the pathological process showed a character of its own. The bone lesions found during life, as also the map-skull, are however produced in this case by a similar process to that occurring in xanthomatosis ossium, e.g. proliferation of reticulum cells of the bone marrow, giving rise to invasion and destruction of the bone.

From the relation between the pathological pale cells and the pre-existing tissue it may safely be deduced, that these cells originated from a proliferation of cell groups present in different organs, which belong to the reticulo-endothelial system. Those cell groups are: in the thymus, the peripheral reticulum formed by the pericytes; in the lungs, the histiocytes in the alveolar septa and in the connective tissue round bronchi and vessels; in the lymph glands, the lymphoid reticulum; in the spleen, the reticulum of the pulp and the peri-adventitial cells; in the bone marrow the myeloid reticulum; in the liver the histiocytes in the peri-portal connective tissue.

Two points need further discussion. First: the necrotic areas found in the thymus, which were surrounded by pavement epithelium and which were regarded as being altered Hassall's corpuscles, have also been observed by others and sometimes have been explained in the same way (Guizetti[6] Siwe[7], Letterer[8], Foot and Olcott[18]).

Second: although several writers on reticulo-endotheliosis have also found cellular proliferation in the lungs (Guizetti, Podvinec and Terplan[9], Siwe, Uher[10]), such proliferation nowhere showed such an unusual picture as found in the present case. It is true that Siwe states that the lungs in his case showed a bullous emphysema, but the nature of this emphysema is not clear from the histological description. This different aspect must be explained by the point of issue of the cellular proliferation, in the present case the bronchial wall, in the others the alveolar septa. In the case described by Guizetti the proliferation originated from the interlobular connective tissue, where perhaps surrounding alveoli have been destroyed, this being the cause and explanation of the finding of air in the soft parts of the neck, in the anterior mediastinum, in the connective tissue of the thymus, and under the visceral pleura.

On the other hand, a picture of the lungs similar to that in the present case has only been described by Apert, Girard and Rappoport[11], in a boy of seven years. Here this condition resembling the bullous emphysema was caused by a destruction of the bronchial walls due to congenital syphilis.

Finally, the question arises as to whether the results of the pathological examination contain some data which can be used to explain the nature of the reticulo-endothelial proliferation. Although, as said before, the macroscopic examination suggested a tumour, this was disproved by the microscopic examination. The cellular proliferation which in different organs originated from different parts of the reticulo-endothelial system appeared to be a reaction to stimulation, for example of an infection. This conception is supported by the fact that another form of reaction, i.e. an exudative one, was found, showing itself in cellular infiltration in lung and liver, while a widespread ' sinus catarrh ' in the lymphatic glands, so often found in generalized infections, also pointed in the same direction. The reticulo-endotheliosis described above might thus be considered to be chiefly a proliferative response to an infectious agent.

At the end of the discussion of the pathological appearances, macroscopic and microscopic, of this disease, the question may be put as to how far the clinician may profit by these results with a view to diagnosing it. From the cases described by Siwe and by Foot and Olcott it may be concluded that puncture of the spleen (Siwe) or biopsy of the spleen (Foot and Olcott) may procure important findings indicating the existence of the disease and that certain related diseases can be excluded in this way. In the present case the result of the examination of the puncture of the nodule behind the left ear might have afforded some indication of the diagnosis, as epitheloid cells and giant cells without tubercle bacilli were found. At that time, however, the possibility of an infective reticulo-endotheliosis was not thought of.

General considerations.

A survey of the cases of reticulo-endotheliosis, published in recent years, which were not caused by a specific infection and did not belong to the lipoidoses—(and this discussion is restricted to the cases observed in childhood*)—shows that the case here reported resembled these in many

*To the cases of reticulo-endotheliosis in childhood mentioned here may be added one described by Borissowa[19] in 1903 under another title. According to the very exact description of the change found, it is now justifiable to say that the patient, a child of nineteen months, suffered from reticulo-endotheliosis with its principal localization in the lymphoid apparatus. Clinical data are missing. Of a case of reticulosis recently observed by Paige in a young child there has only appeared an abstract[21] so far.

respects but also showed many differences. In table 2 a summary is given of the most important clinical and histological details in cases in the literature. The similarity lies first of all in the age at which the first symptoms are observed. As in Niemann-Pick's disease and in Schüller-Christian's disease

TABLE 2.—SUMMARY OF THE MOST IMPORTANT CLINICAL AND HISTOLOGICAL FINDINGS IN ANALOGOUS CASES.

Name of the author	Age of the patient	Duration of disease	Beginning of disease	Clinical course								Histological changes					
				Fever	Necrotic sore throat	Haemorrh. diathesis	General swelling of lymphglands	Hepatomegaly	Splenomegaly	Anaemia	Change in blood picture	Thymus	Bone marrow	Spleen	Lymph glands	Lungs	Liver
Letterer, 1924	6 mths.	4 days	abscess, sepsis	+	—	+	+	+	+ +	—	+	+ +	+	+ +	+ +	?	+
Akiba, 1926 ...	10 mths.	6 wks.	fever, purpura	+	+	+	+	+	+ +	+	?	?	?	+ +	+ +	—?	+
Krahn, 1926 ...	5 yrs.	6 mths.	sepsis	+	—	+	+	—	+ +	+	small	?	+ +	+ +	+ +	—?	+ +
Sherman, 1929	11 days	4 days	dyspepsia, jaundice, erysipelas	+	—	—	—	+	+	+	—	?	+	+	?	?	+
Guizetti, 1931	3 mths.	20 days	coughing, fever, epistaxis	+	—	+	+ ?	+ +	+ +	+	—	+ +	+ +	+ +	+ +	+ +	+ +
Podvinec and Terplan, 1931	1 year	16 days	ill-looking, fever	+	+	+	+	+ +	+ +	—	—	?	+ +	+ +	+ +	+	+
Uher, 1933 ...	1¾ yrs.	17 days	sore throat, fever	+	+	+	+	+	+	—	small	?	+	+ +	+ +	+	+
Siwe, 1933 ...	16 mths.	3 mths.	swelling of left leg	+	—	+	+	+	+	—	small	+ +	+ +	+ +	+	+ +	+ +
Gittins, 1933 *a*	2-3 yrs.	22 mths.	anaemia	+	—	+ +	—	+	+	+ +	small	?	+ +	+ +	+ +	—	+
b	21 mths.	3 wks.	anaemia, abscesses	+	—	+	+	—	+	+ +	+	—?	+ +	+ +	+ +	—?	+
c	1 year	11 days	anaemia	—?	—	—	+	+ +	+ +	+ +	+	?	—	+ +	+	—?	+
d	17 wks.	4 mths.	anaemia	—	—	small	+	+	+ +	+ +	+	?	+	+ +	+	?	+
Klostermeyer, 1934	13 mths	7 wks.	swelling of the face	+	+	—	+	+ +	+ +	+	agranulocytosis	+	+	+	+ +	+	+
Foot and Olcott, 1934	2¾ yrs.	1 year	purpura, otitis media	—	—	+	—	+ +	+ +	—	+	+ +	+ +	+	+ +	+ ?	+
Roussy and Oberling, 1934	8 mths.	12 days	purpura	+	—	+	+	+	+ +	+	small	?	+	+ +	+ +	?	+ +
Authors' case	4 mths.	8 wks.	otitis media	+	—	—	+	+	+	—	small	+ +	+ +	+	+	+ +	+

Meaning of the signs in the histological changes:
— = nothing has been found.
? = nothing is stated.
+ = slight changes.
+ + = distinct changes.

the patients are for the most part young children; so that the impression is again obtained that in young children the reticulo-endothelial system reacts readily to stimulation. A second point of agreement lies in the fact that some form of infection in the aetiology can hardly ever be denied; thus the first symptoms of the disease were often observed following an acute infectious disease. As observed in cases of xanthomatosis in childhood acute otitis media often preceeded the disease (as in the present case) or soon after the beginning of the disease otitis media occurred (Letterer) or this was found at the autopsy after a short course of the disease (Podvinec and Terplan). A necrotic type of sore throat (Akiba[12], Podvinec and Terplan, Uher, Klostermeyer[13]) was often present at the onset. Repeatedly the clinical course pointed to sepsis as a cause of the disease by the presence of fever, enlargement of spleen and lymph nodes, and the presence of a haemorrhagic tendency. The course of the disease is mostly short, often only two to three weeks, but sometimes months or even years. In a case described by Sherman of an infant eleven days old, the disease (dyspepsia, infective jaundice, erysipelas) lasted only four days. At the necropsy no real reticulo-endothelial proliferation was found but an enormous swelling and partial necrosis of reticulo-endothelial cells, with intensive phagocytosis of streptococci.

In the present case an infectious basis for the proliferation of the reticulo-endothelial system must seriously be considered. The result of the pathological examination supports this conception as already indicated, but the clinical picture is also in favour of this as shown by the otitis media which preceded the disease, the fever which remained throughout the disease although the otitis media diminished in severity, and the slightly infective type of blood picture. The cultural and bacteriological investigations were totally negative. The infective origin of the disease cannot be excluded on this ground, just as this is not absolutely proved by the fact that in other cases at the necropsy accumulations of cocci were found in different organs (Guizetti, Uher), and during life bacteria were cultivated from the blood (Foot and Olcott, Sherman). All these facts make it highly probable that an infection was the cause of the reticulo-endotheliosis in our case. There is no evidence here to point to a primary disturbance of metabolism as is the case in the lipoidoses which are also often associated with bone defects. In this connection too much stress must not be laid on the increase of the cholesterol content of the blood found in the present case shortly before death.

As the disease under discussion so often affects the reticulum of the haemopoietic organs, the results of blood examinations in the different cases published have been studied with great interest. These results reveal no constant feature. In some cases there was the picture of an acute or chronic, regenerative or aplastic anaemia (Gittins[14], Krahn[15]). In most cases there was no or only a slight secondary anaemia. As a rule the number of leucocytes was normal or slightly increased. Sometimes there was a distinct leucopenia (Foot and Olcott); rarely there was a definite leucocytosis. The

white blood picture showed little change. Klostermeyer's case ran the course of an agranulocytosis; sometimes there was a moderate monocytosis or a picture that resembled acute leukaemia.

Finally, mention must be made of the localization of the changes found clinically and at the pathological examination; these localizations differed greatly in the various cases. Mostly the disease affected the lymphoid apparatus, spleen and lymph nodes. This localization, combined with the blood picture, in some cases gave rise to the clinical diagnosis of anaemia pseudo-leukaemia infantum of von Jaksch. In one case (Klostermeyer) the anatomical picture resembled of typhoid fever, though histological and bacteriological investigation did not confirm this. Less frequently and to a lesser extent the reticulo-endothelial system in the liver, lungs and bone marrow was affected. Clinically the spleen and liver enlargement (with a number of accompanying symptoms) may be prominent, which must be remembered in the differential diagnosis of this combination. This was stressed particularly by Siwe. In the cases described by Letterer and recently by Roussy and Oberling[20], which otherwise ran a similar course, changes in the skin were noticed.

As regards the localization of the process the present case was a most unusual one. Not so much because of the appearance of the lungs, for this could be explained readily by the peculiar localization of the reticulo-endothelial proliferation in the lungs, but because of the bone changes; their presence and enormous extension could be observed clinically. In this extension and in this form they have not been observed in analogous cases. Their origin must have a similar explanation as, for example, in xanthomatosis. Guizetti and Siwe also observed changes in the bones in their cases during life, but only in the right humerus and left fibula respectively; in one of his patients Gittins found at the x-ray examination and at the autopsy slight changes in the bones. In the case described by Foot and Olcott the changes in the bones were more extensive; there were lesions in the spine, causing kyphosis, which fact had suggested the diagnosis of Pott's disease; the same has occurred sometimes in xanthomatosis (Anspach). Usually the bone changes are only found at the histological examination. The case of Schultz, Wermbter and Puhl[16] with skull defects and exophthalmus has not been considered in our study, because doubt has been expressed as to whether this was a pure case of infective reticulo-endotheliosis or not; it might either be an example of xanthomatosis in a later stage, or of lymphogranulomatosis.

It is remarkable that the bone changes found in the present case and also in those of Guizetti, Siwe and especially of Foot and Olcott, were associated with an extensive destruction of the thymus tissue caused by the reticulo-endothelial proliferation. Is this a remarkable coincidence, or is there some relation between the intensity of the bone changes, situated often near the epiphyses and in the absence of a hormonal influence which, as is now accepted, is exercised by the thymus in young individuals upon the development of the bones? For the present

a definite reply to this question cannot be given. The combination of thymic and bony changes is also interesting from another point of view. The thymus in general is rarely diseased, yet it is frequently affected in the rare condition of reticulo-endotheliosis. Perhaps the malady here discussed is a specific infection with a particular affinity for the thymus. In every case it seems desirable that in the clinical and histological examination of similar patients special attention should be paid to the thymus, with a view eventually to a clearer classification of these particular affections. This means that the possibility of the existence of reticulo-endotheliosis with particular localization in the thymus must also be considered in the clinical investigation of young children who show infective symptoms combined with x-ray changes in bone, and in whom there is no reason to accept the existence of a primary disturbance in metabolism.

Summary.

The clinical picture and the detailed autopsy findings in a child aged four months are described with a diagnosis of reticulo-endotheliosis. The cause of the proliferation of the reticulo-endothelial system is attributed to an infection. Clinically extensive bone changes with development of a map skull were prominent. Pathologically an unusual localization of the process in thymus and lungs was found; in the lungs this had given rise to a very unusual picture. The clinical findings and those found after death are compared with those found in a number of analogous cases published in recent years.

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THE GASTRIC SECRETION IN ANAEMIA

BY

JESSIE W. OGILVIE, B.Sc., M.B., Ch.B., D.P.H.*
(From the Department of Paediatrics, Glasgow University, and the Biochemical Laboratory, Royal Hospital for Sick Children, Glasgow.)

It is well known that anaemia of the Addisonian type is accompanied by an absence of free hydrochloric acid from the gastric juice.

In so-called secondary anaemia Davies[1] found that in the gastric juice there was excess of mucus, low peptic activity and frequently a fixed pH in contrast with the absence of mucus and peptic activity and complete fixation of the pH in pernicious anaemia. Hartfall and Witts[2] pointed out that in simple achlorhydric anaemia the total chlorine and peptic activity were low when there was a deficient amount of intrinsic factor. Recently Hartfall[3] has stated that in the same individual free acid may be secreted at one time and not at another. He also considered that the data obtained from infants were unreliable owing to the numerous inhibitory factors likely to interfere with gastric secretion. In twenty-six adult patients with unexplained achlorhydria Polland[4] failed to find any significant variation from normal in the haemoglobin value and red cell count; he therefore concluded that anacidity per se did not tend to the production of anaemia. Bloomfield and Keefer[5] as a result of their investigations into gastric secretion in adults decided that anaemia, other than the pernicious type, had little or no influence on the secretion of gastric juice. Hawksley, Lightwood and Bailey[6] in thirteen children under ten years of age with simple iron-deficiency anaemia found achlorhydria in twelve, and consider that achlorhydria may be a causal factor. In the literature there are few other studies in children of the association of anaemia with defective gastric secretion.

During the course of an investigation into the gastric secretion in children, the following results were obtained. Thirty-four anaemic children, twenty-two boys and twelve girls, were examined; the ages varied between five months and eleven years. The method employed in examining the gastric secretion has been described in previous papers[7]. In children, as in adults, there is wide variation in the concentration of the hydrochloric acid in the gastric juice but for purposes of classification any readings of an acidity above 50 c.c. or below 12 c.c. $\frac{N}{10}$ per cent. were considered to indicate hyper- or hypochlorhydria respectively.

Results

Free hydrochloric acid.—The maximum free hydrochloric acid varied from nil to 55·6 c.c. $\frac{N}{10}$ per cent. with a mean value of $20{\cdot}3 \pm 2{\cdot}9$, which is significantly $(11{\cdot}2 \pm 3{\cdot}3)$ lower than that obtained in a normal group. When the patients are considered in age groups it is clear

* This work was done during the tenure of a McCunn Medical Research Scholarship.

that the greatest reduction in acid is present in the fourth or oldest group (nine to twelve years). In the third (six to nine years) the mean value is actually greater than in normal children of the same age. Six patients had achlorhydria at the first test, seven had hypochlorhydria and four hyperchlorhydria. None of the last group, however, showed a free hydrochloric acid content of over 57 c.c. $\frac{N}{10}$ per cent. In only seventeen was the free hydrochloric acid found to be within normal limits.

TABLE 1.

ACHLORHYDRIA.

Name	Age in years	Sex	Type of anaemia	Blood picture			Blood chlorine c.c. $\frac{N}{10}$	Gastric analysis (max. fig.)			
				R.B.C. millions	Haemoglob. per cent.	C.I.		HCl. c.c. $\frac{N}{10}$	Total acidity c.c. $\frac{N}{10}$	Total Chlorine c.c. $\frac{N}{10}$	Peptic activity units
J.C. ...	$1\frac{1}{12}$	M.	?Acholuric	2·2	35	·8	95·22	nil.	41·1	96·2	—
G.P. ...	$2\frac{3}{12}$	M.	Nutritional	3·1	30	·5	—	nil.	20·5	97·5	62·5
								nil.	6·2	81·3	10·0
								*nil.	8·2	79·8	8·1
	$2\frac{4}{12}$			3·9	40	·5	—	18·3	30·4	77·2	6·4
A.B. ...	$2\frac{4}{12}$	M.	Nutritional	4·4	72	·8	70·68	nil.	42·0	69·5	1·6
A.McM.	$2\frac{4}{12}$	F.	Haemolytic	2·1	15	·4	93·93	nil.	20·0	89·9	25·6
				3·9	42	·5	—	12·0	22·0	68·7	28·9
				4·6	78	·9	74·46	nil.	36·1	54·6	6·4
	$2\frac{6}{12}$				75		—	nil.	29·6	83·1	10·0
								* nil.	24·5	69·2	14·4
								* nil.	21·1	67·6	40·0
J.T. ...	$2\frac{6}{12}$	M.	Von Jaksch	3·8	45	·6	—	nil.	19·3	69·2	—
T.C. ...	$6\frac{6}{12}$	M.	Nutritional (bowel deformity)	2·8	35	·6	84·80	nil.	23·3	66·3	—

* After histamine.

Of the six children with achlorhydria three had simple iron-deficiency anaemia, one acholuric jaundice, one haemolytic anaemia and one von Jaksch's anaemia. One of the children (T. C.) with iron-deficiency anaemia died a week after the test; at the post-mortem examination a mesenteric cyst and duplication of a portion of the ileum were found. Another (G. P.) at first gave no free hydrochloric acid response even after histamine but a month later a concentration of 18·3 c.c. $\frac{N}{10}$ free hydrochloric acid was found after the ordinary gruel test meal. The other patient (A. B.) made a good recovery with iron treatment. The child with von Jaksch's anaemia (J. T.) made a good recovery but owing to the fact that he was soon transferred to a convalescent home, only one test was made. The child with acholuric jaundice (J. C.) had a red cell count of 2,190,000 per c.mm., haemoglobin

33 per cent. and definitely increased fragility (occuring in 0·56 per cent. NaCl). Eventually he contracted pneumonia from which he died; only one test of the gastric secretion was carried out. The patient with haemolytic anaemia of unknown origin (A. McM.) had achlorhydria on the first test. After iron treatment for three weeks the gastric analysis showed a concentration of twelve c.c. $\frac{N}{10}$ free hydrochloric acid, but in four subsequent tests, two with histamine, it was impossible to detect free hydrochloric acid in the gastric juice in spite of treatment with iron, marmite and liver; the anaemic condition had meanwhile greatly improved the red cells having risen to five millions per c.mm. and the haemoglobin to 80 per cent.

TABLE 2.

HYPOCHLORHYDRIA.

Name	Age in years	Sex	Type of anaemia	Blood findings			Blood chlorine c.c. $\frac{N}{10}$	Gastric analysis (max. fig.)			
				R.B.C. millions	Haemoglob. per cent.	C.I.		HCl. c.c. $\frac{N}{10}$	Total acidity c.c. $\frac{N}{10}$	Total chlorine c.c. $\frac{N}{10}$	Peptic activity units
J.K. ...	$8\frac{1}{12}$	M.	Nutritional	5·9	50	·4	83·83	10·2	87·1	70·7	—
J.M. ...	$1\frac{2}{12}$	M.	Nutritional	4·5	58	·6	91·80	4·4	33.4	91·8	67·6
H.J. ...	$1\frac{3}{12}$	F.	Haemolytic	4·3	70	·8	79·57	8·4	34·7	74·1	22·5
E.G. ...	$3\frac{4}{12}$	F.	Nutritional	3·6	70	1·0	76·50	9·3	18·5	132·6	6·4
A.G. ...	$3\frac{7}{12}$	M.	Aplastic	3·7	62	·9	—	8·5	26·8	60·1	—
A.C ...	9	M.	Nutritional	3·9	42	·5	89·38	5·6 3·9*	16·7 18·5	53·4 71·9	0·9 2·5
H.McK.	$9\frac{8}{12}$	M.	Nutritional	4·9	60	·6	80·32	11·6	25·2	68·5	—

* After histamine.

TABLE 3.

HYPERCHLORHYDRIA.

Name	Age in years	Sex	Type of anaemia	Blood findings			Blood chlorine c.c. $\frac{N}{10}$	Gastric analysis (max. fig.)			
				R.B.C. millions	Haemoglob. per cent.	C.I.		HCl. c.c. $\frac{N}{10}$	Total Acidity c.c. $\frac{N}{10}$	Total Chlorine c c. $\frac{N}{10}$	Peptic activity units
D.K. .	$1\frac{8}{12}$	M.	Nutritional	4·4	40	·5	—	51·2	80·1	113·2	28·9
J.McN.	$2\frac{9}{12}$	M.	Haemolytic	4·1	55	·7	—	54·5	75·6	95·4	108·9
G.M. ...	8	F.	Aplastic-haemolytic	0·6	15	1·2	96·96	50·0	66·7	76·8	19·6
R.B. ...	$10\frac{6}{12}$	F.	Acholuric jaundice	2·7 3·7	58 68	1·1 ·9	84·94 —	55·6 56·7	72·3 64·5	111·1 99·8	52·9 19·6

There were seven patients with hypochlorhydria; five of them had simple iron-deficiency anaemia, one haemolytic and one aplastic anaemia.

In four hyperchlorhydria was found. In one of them (G. M.) there was evidence of extreme haemolytic anaemia with a red cell count of 630,000 and a haemoglobin concentration of 15 per cent. In another (R. B.) with acholuric jaundice it was found that three weeks after splenectomy there was no change in the hyperchlorhydria although there was great improvement both in the general condition and the condition of the blood. A third (D. K.)

TABLE 4.

NORMAL ACID SECRETION.

Name	Age in years	Sex	Type of anaemia	Blood findings			Blood Chlorine c.c. $\frac{N}{10}$	Gastric analysis (max. fig.)			
				R.B.C. millions	Haemoglob. per cent.	C.I.		HCl. c.c. $\frac{N}{10}$	Total acidity c.c. $\frac{N}{10}$	Total Chlorine c.c $\frac{N}{10}$	Peptic activity units
T. McF.	$1\frac{5}{12}$	M.	Nutritional	3·3	40	·6	92·82	20·5	30·7	93·8	—
A.M. ...	$1\frac{5}{12}$	M.	von Jaksch	4·2	44	·6	82·23	17·5	61·4	69·9	—
R.McR.	$1\frac{8}{12}$	M.	Nutritional	4·5	46	·5	79·80	15·0	42·5	73·5	102·4
J.McI.	$1\frac{10}{12}$	M.	Nutritional	3·8	24	·3	—	15·2	27·9	69·4	25·6
E.B. ...	$1\frac{4}{12}$	F.	Nutritional	5·0	62	·6	—	20·0	50·0	66·1	40·0
A.McC.	$1\frac{4}{12}$	M.	Nutritional	4·7	46	·5	82·82	18·0	45·0	73·7	176·4
C.McK.	$1\frac{4}{12}$	F.	von Jaksch	4·1	45	·9	80·01	22·4	32·0	57·7	—
G.C. ...	$1\frac{9}{12}$	M.	Nutritional	3·5	44	·6	—	30·0	44·0	81·8	22·5
J.McK.	2	M.	Nutritional	3·7	25	·3	79·68	12·7	28·6	74·9	—
H.C. ...	$3\frac{6}{12}$	M.	Nutritional	3·0	52	·9	75·14	18·1	59·3	76·0	—
D.McM.	4	F.	Nutritional	3·8	82	1·1	72·80	43·3	57·5	81·2	16·9
M.A. ...	6	F.	von Jaksch	3·5	50	·7	81·16	38·4	51·2	—	152·1
M.V. ...	$7\frac{6}{12}$	F.	Haemolytic	2·4	50	1·1	99·45	37·1	50·7	90·3	78·4
W.W.	$8\frac{6}{12}$	F.	Haemolytic	1·7	32	·9	95·18	39·4	56·8	95·1	96·1
J.H. ...	10	M.	Aplastic ...	1·1	17	·8	–	24·2	32·3	53·9	—
J.J. ...	10	M.	Nutritional	4·9	52	·5	74·10	33·2	39·8	55·8	—
A.B. ...	11	F.	Nutritional	1·6	25	·8	90·90	15·4	33·3	88·9	—

had simple iron-deficiency anaemia dating from early infancy and probably associated with prematurity. The fourth (J. McN.) had mild jaundice with urobilinuria, a red cell count of 4,000,000 per c.mm. and a haemoglobin content of 50 per cent.

Of the seventeen patients whose gastric secretion fell within normal limits the anaemia in nine was of the simple nutritional type; in three it was considered to be of the von Jaksch type, in two haemolytic, in one aplastic

and in two it was impossible to relegate the condition into any special category. In one of the unclassified group (G. C.) there was great enlargement of the liver and a red cell count of 3,500,000 and haemoglobin 44 per cent. In the other (D. McM.) the red cells numbered 3,800,000 and haemoglobin was 82 per cent. Of the children with normal secretion two died. One of them (J. H.) had an aplastic anaemia (red cells 1,000,000 and haemoglobin 12 per cent.) which did not respond to repeated blood transfusion. The other (W. W.) had a greatly enlarged liver possibly due to a neoplasm, deep jaundice, bile and urobilin in the urine, a biphasic van den Bergh reaction in the serum and a profound anaemia of the hyperchromic, macrocytic type; this case has been classified under the haemolytic group.

From these results it does not appear that there is any relationship between the amount of free hydrochloric acid in the gastric secretion and the degree of anaemia (red cell count and haemoglobin) nor do any of the types studied show any constant change in the secretion of free acid (table 5).

TABLE 5.

SHOWING THE RELATIONSHIP OF THE TYPE OF ANAEMIA TO THE FREE HYDROCHLORIC ACID SECRETION

	Iron deficiency	Acholuric	Von Jaksch	Haemolytic	Aplastic	Unclassified
Achlorhydria ...	3	1	1	1	—	—
Hypochlorhydria ...	5	—	—	1	1	—
Normal secretion ..	9	—	3	2	1	2
Hyperchlorhydria ...	1	1	—	2	—	—

Total acidity.—The maximum figures varied between 16·7 to 87·1 c.c. $\frac{N}{10}$ per cent. with a mean value of 42·5±3·3 which was significantly lower by 7·6±2·0 than the mean of the normal group.

Total chlorine.—The maximum value for the total chlorine of the gastric secretion varied between 53·0 to 132·6 c.c. $\frac{N}{10}$ per cent. with a mean value of 79·6±3·0 which was similar to that found in healthy children. The mean value for blood chlorine, however, was significantly higher by 9·29±5·5 than that of the healthy group and varied inversely with the red cell count. The high mean value of blood chlorine is presumably due to the relative increase in plasma volume. It is possible, therefore, that the apparently normal values found for the total chlorine of the gastric secretion were not really the result of normal secretion but were due to the increased amount of chlorine in the blood passing through the gastric mucosa. If this is not the case one must assume that in the present series only the secretion of free hydrochloric acid was affected. This latter view is supported by the fact that the mean value for peptic activity did not differ significantly from normal. In pernicious anaema, on the other hand, where the peptic activity is markedly deficient, Miller and Smith[8] and Wilkinson[9] found that the

concentration of total chlorides in the gastric secretion was below the average obtained in individuals with normal secretions.

Emptying time.—The average emptying time was longer than in the control group. In fourteen patients starch could still be detected in the gastric contents at two hours.

The relationship of the type of anaemia to the free hydrochloric acid secretion

It is recognized that the concentration of free hydrochloric acid in the gastric juice has a direct relationship to the capacity for absorbing iron. For this reason it might be anticipated that diminution or absence of free hydrochloric acid would be found in cases of simple anaemia where low haemoglobin percentage was the prominent feature. This has been found in the present series.

Of the thirteen cases in which there was defective secretion of hydrochloric acid (achlorhydria or hypochlorhydria) eleven had hypochromic anaemia as measured by a colour index which did not exceed 0·8. This suggests that hydrochloric acid deficiency strongly favours the production of hypochromic anaemia but that other causes, for example iron starvation, must play a part because ten out of eighteen cases of iron deficiency anaemia showed no diminution in hydrochloric acid secretion (table 5).

Summary

The results of fractional gastric analysis in a series of thirty-four children with anaemia show that there is in many cases a marked diminution in the secretion of free hydrochloric acid and in total acidity. The other constituents of the gastric juice do not differ significantly from those of a normal series.

No correlation was noted between either the number of red cells or the haemoglobin and the maximum secretion of free acid.

There seems to be a close association between defective secretion of hydrochloric acid and the hypochromic type of anaemia.

I desire to thank Professor G. B. Fleming and Dr. N. Morris for their helpful criticism during this investigation. I also wish to acknowledge the gift by Messrs. Parke Davis & Co. of the histamine phosphate used for the patients referred to in this paper.

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A CASE OF COELIAC DISEASE SHOWING UNUSUAL FEATURES SUCCESSFULLY TREATED WITH INSULIN AND GLUCOSE

BY

BERNARD SCHLESINGER, M.D., F.R.C.P.,

AND

K. D. KEELE, M.D., M.R.C.P.

(From the Children's Department, Royal Northern Hospital.)

The following case, clinically typical of coeliac disease, is remarkable in that the brunt of the metabolic error falls on carbohydrate rather than on fat metabolism.

History. S. T., male, aged seven years, was first seen in June, 1934, complaining of vomiting. This had begun some months ago and occurred in bouts every two or three weeks, lasting for one day. During this time the abdomen had been noticed to swell. The bowels had always been ' loose.'

Past history. He was a full-time child, never breast fed, and various foods had been tried. He talked and teethed normally, walked at three years and was always stunted.

Family history. Other children healthy; one died of ' fits.' The mother had one miscarriage. The home environment was poor.

On examination (June, 1934), the patient was a stunted child with a large abdomen and wasted buttocks (fig. 1). He was mentally listless. His weight was 1 stone 9 lb. (Normal for age, 2 st. 12 lb.). Signs of active rickets were found clinically and radiologically. Skiagrams also showed multiple, symmetrical fractures of both ulnae and fibulae (fig. 2). An x-ray of skull showed a normal pituitary fossa.

Special investigations. The tuberculin (Mantoux test) was negative. A blood count showed:—

R.B.C., 5,200,000 per c.mm.; Hb., 72 per cent.; C.I., 0·65; W.B.C., 14,000 per c.mm.

Differential count: Polys., 6,160 (44 per cent.); lymphos., 7,140 (51 per cent.); monos., 280 (2 per cent.); eosins., 420 (3 per cent.). Nucleated reds 280 per c.mm. Anisocytosis and polychromasia were present. The blood urea was 34 mgm. per cent. The van den Bergh direct test was negative, the indirect test 0·5 unit. The clinical findings were as follows:—

BEFORE INSULIN TREATMENT:—Blood calcium, 10·1 mgm. per cent.; blood phosphorus, 1·4 mgm. per cent.; blood sugar curve (see fig. 4 (a)) max. rise, 5 mgm. per cent.

Fat analysis of faeces (fat of diet, 13 gm. daily): Split fat, 17 per cent.; unsplit fat, 8 per cent.; total fat, 25 per cent. Repeated fat analysis, total fat, 14 per cent.

AFTER INSULIN:—Blood calcium, 10 mgm. per cent.; blood phosphorus, 6·4 mgm. per cent.; blood sugar curve max. rise, 30 mgm. per cent. (fig. 4 (b)). Fat analysis of faeces (fat of diet 78 gm.): Split fat, 14 per cent.; unsplit fat, 6 per cent.; total fat, 20 per cent.

Ossification. The outstanding defect in mineral metabolism lay in the poor ossification. Active rickets was present and osteoporosis had reached such a degree that both ulnae and fibulae—the more

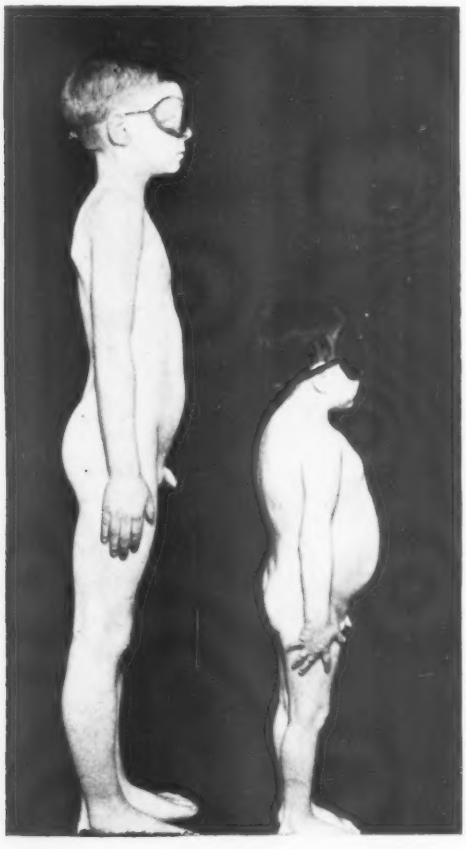

FIG. 1.—Photograph of patient with normal boy of same age (8 yr.). Note the protuberant abdomen and wasted buttocks.

slender long bones—showed symmetrical fractures. It was noteworthy that even when first seen callus had begun to form. The blood calcium, also, was normal (10·1 mgm. per cent.), no doubt in response to the vitamin therapy which had already been in progress for a week or more prior to the chemical investigations. Blood phosphorus, on the other hand, was still markedly deficient, and the picture presented was strikingly that of low phosphorus rickets (Gestenberger).

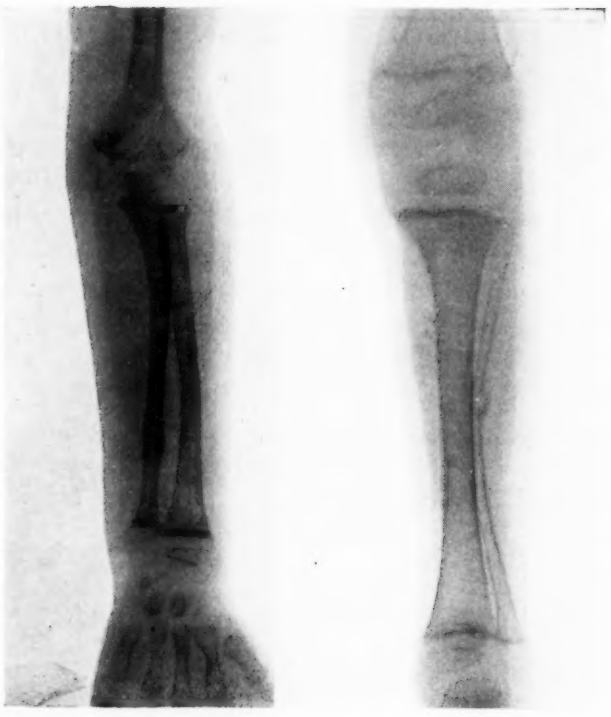

FIG. 2A.—Skiagrams of bones in leg and arm on admission, showing active rickets and multiple symmetrical fractures.

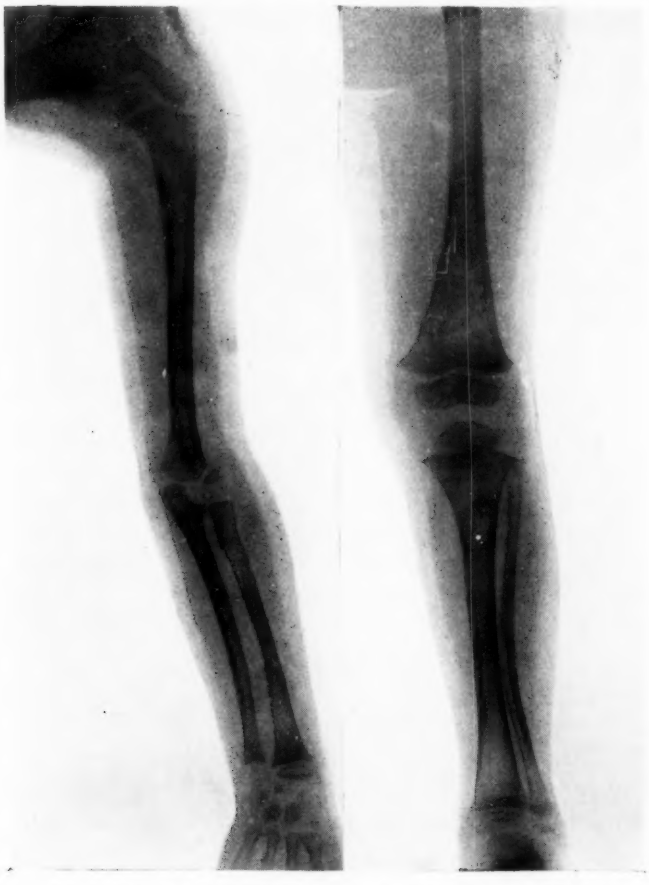

FIG. 2B.—Skiagrams of bones 6 months later. The fractures are united. The rickets is healed.

Progress and treatment.

Progress is most clearly depicted by the weight chart (fig. 3). Here it is evident that at first, despite a low fat diet, ultra-violet light, calcium and radiostoleum, loss of weight continued steadily for eight weeks, amounting to 3 lb. 12 oz. On beginning insulin and glucose therapy (insulin 3 units, glucose 1·5 gm. twice daily), immediate improvement was noticed, with a gain of 4 lb. 12 oz. in seven weeks. Two control periods (' a ' and ' b ' on weight chart) are consistent with the fact that this gain in weight was due to the treatment.

The gain in weight was accompanied by general clinical improvement, and the whole mental outlook became brighter. The stools were less frequent, firmer and no longer offensive. Their total fat content remained

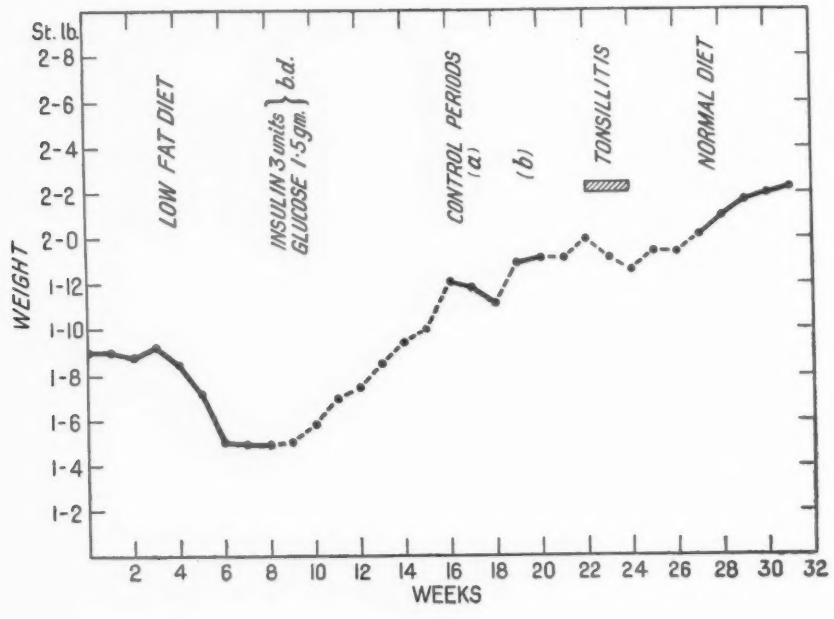

Fig. 3.

——— = No insulin.
- - - - - - = Insulin.

normal. At the same time the blood phosphorus rose to 6·4 mgm. per cent.—an unusually high figure. Estimation of the blood sugar no longer showed a flat curve but a more normal rise of 30 mgm. per cent. (see fig. 4 (b)).

Further metabolic studies.

On the grounds of a normal fat content of the faeces criticism might be raised as to the diagnosis. In every other way the case was typical of coeliac disease and we know of no other disorder in which a large abdomen, wasted buttocks, unhealthy stools, rickets and infantilism, are associated.

Carbohydrate metabolism.—The most striking feature of the case was the disordered carbohydrate metabolism. As already stated, a blood sugar curve, with the patient on an ordinary diet and receiving no treatment, was almost flat. On repeating the investigation after a few days' regular administration of glucose and insulin, there was a definite change in the shape of the curve approaching the normal. Finally, after an interrupted treatment of seven weeks, during which the child's general condition showed a dramatic improvement, the insulin and glucose were stopped and an ordinary diet resumed. This did not in any way interfere with his progress.

It was noticed that in spite of the definite clinical improvement, the blood sugar curve reverted to the flat type, not only following the administra-

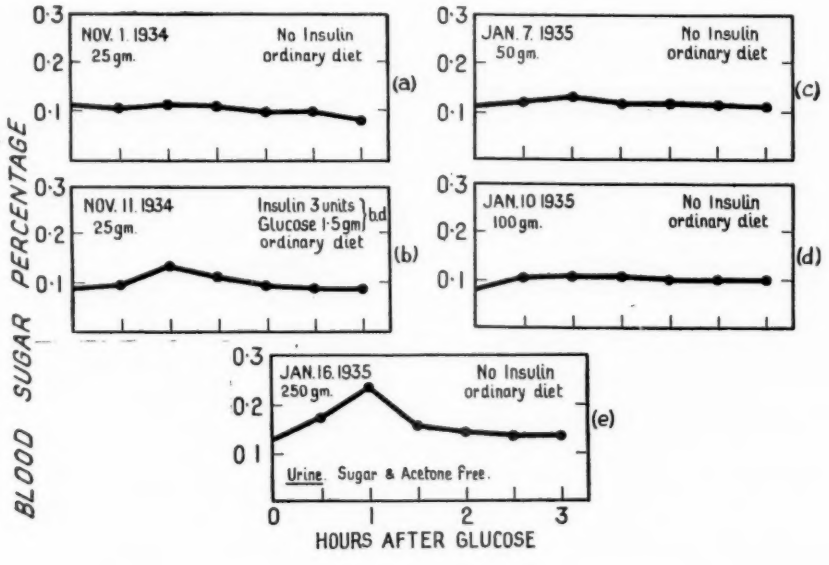

FIG. 4.

tion of 25 gm. of glucose by the mouth, the usual standard employed in the test at that age, but even after doses as high as 50 and 100 gm. It was only when 250 gm. was administered—an extraordinary dose—that a reasonable rise in the blood sugar was observed (to 225 mgm. per cent.) (fig. 4 (e)). There was no glycosuria.

Experiments were undertaken to ascertain whether the flat blood sugar curves were due to faulty carbohydrate assimilation. An ordinary diet was given to which was added 100 gm. of glucose daily for three days. After a suitable period the experiment was repeated using 250 gm. of glucose. The passage through the intestines was followed in each case by a marker (charcoal) and the faeces collected and analysed for soluble carbohydrate. At the same time the blood sugar

estimations were carried out to which we have already referred. Urine tests throughout the experiment showed the absence of glycosuria. Had there been any faulty carbohydrate assimilation from the alimentary tract present, we would have expected to find a greater quantity of unabsorbed carbohydrate in the faeces following the larger amount of glucose ingested in the second experiment. This did not take place and in both instances the faecal carbohydrate was negligible—over 97 per cent. being absorbed. Lack of absorption from the digestive tract cannot therefore account for the flat blood sugar curves.

Discussion.

In discussing the aetiology of coeliac disease, emphasis in the past has been laid on errors of fat metabolism, the essential fault lying in a defect in fat absorption. According to Morris and Macrae[1] there is in health an unlimited absorptive power for fat. In patients with coeliac disease, on the other hand, though there is a rise in absorptive power with a rise in fat intake, this is limited, so that on a high fat diet excess appears in the stools. In the present case the fat content of the faeces did not increase, though the fat in the diet was raised from 13 gm. to 78 gm. So for this rise, absorptive power increased normally.

It has been suggested by Moncrieff and Payne[2] that the blood fat is abnormally high in coeliac disease and that the excess in the stools represents an overflow, much in the same way as glycosuria is an overflow of the blood sugar. This attractive theory has not met with general acceptance. Up to the present, no one has paid great attention to abnormalities in carbohydrate metabolism in regard to the aetiology of the disease. Nevertheless, flat blood sugar curves are well recognized[3, 4, 5]. So constant is this phenomenon that Morris and Macrae state that ' the low blood sugar curve seems to be pathognomonic of the active stage of coeliac disease.'

There are two obvious ways of interpreting this flat blood sugar curve. It may either be due to an increased glycogenic function of the liver, or to a defective absorption from the intestine. Hepatic function as far as carbohydrate is concerned has been found normal[1] and there are objections to the theory of a defective intestinal absorption. These have been raised by Thaysen and Norgaard[5] on the grounds that (1) the blood sugar curve remains low after intravenous injections of glucose, (2) the respiratory quotient rises to unity after dextrose injection, and (3) the R.Q. is higher on a carbohydrate diet than on a mixed one. They conclude that the error must be one of metabolism of glucose, not assimilation, and endeavour to explain this on the basis of an endocrine dysfunction.

We realize that the absorption theory has many supporters, in particular Macrae and Morris, but our experience with the present case does not bear this out. The power of alimentary assimilation appeared to be unimpaired; yet the blood sugar curve did not show the normal rise and remained flat

even after the injection and satisfactory absorption of quite large quantities of glucose. The beneficial influence of insulin both on the blood-sugar curve and the patient's general condition seem to lend strong support to an endocrine disorder in coeliac disease.

There is as yet insufficient evidence to implicate any particular endocrine gland, although the pancreas has always been under suspicion. Poynton and Cole[6] have described an isolated instance of coeliac disease with glycosuria. There, however, the pancreatic dysfunction led to an upset of carbohydrate metabolism quite opposite to that observed in our case. Experimentally ligature of the main pancreatic duct in dogs has produced a flat sugar curve[5]. In man it is the faulty action of the pituitary body rather than of the pancreas that is associated with the type of sugar curve under consideration.

Insulin therapy has been used successfully by others in the treatment of coeliac disease (Bellingham-Smith[7]; Budde[8]). Both observers were impressed by the dramatic response particularly as regards the weight and the character of the stools.

Coeliac disease is a vague term inasmuch as it indicates nothing further than a disease of the bowel. It is generally held to be primarily a disorder of fat metabolism. Carbohydrate metabolism in our opinion has always been allowed to remain too much in the background of the many researches into the aetiology. On the clinical side, the sudden losses of weight and the equally surprising gains, without any apparent alteration in the stools, could best be explained by an inconstant tissue sugar content and a corresponding irregular storage of water. Finally, we have been impressed by the benefit obtained in desperate cases by the subcutaneous injection of glucose-saline.

Summary.

1. A patient with clinically typical severe coeliac disease is described, with rickets and symmetrical fractures.

2. Fat analysis of the stools was normal.

3. The brunt of the disorder appeared to be bound up with a faulty carbohydrate metabolism.

4. Marked clinical improvement was obtained with insulin and glucose therapy.

5. The bearing of this and other similar cases in the literature on the aetiology of the disease is discussed. A tentative suggestion is made that a significant part is played by a disordered endocrine system.

Our thanks are due to Dr. Ellison and Dr. Mackenzie of the pathological department for their invaluable co-operation in the investigations of this case.

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REMARKS ON HEREDITY IN RELATION TO TUBERCULOSIS *

BY

G. GREGORY KAYNE, M.D., M.R.C.P.(LOND.).

The literature on the relation of heredity to tuberculosis is extensive. An attempt will be made here to deal with the main arguments, particularly those of the more recent work in France. For a comprehensive survey of the subject at the end of the last century the reader is referred to Küss[20].

The relation of heredity to tuberculosis must be considered in two aspects: (a) inheritance of seed, (b) inheritance of soil. By the former is meant the transmission from the parent to the child of tubercle bacilli or other biological variety of the virus. This may show itself (1) as ' evident congenital tuberculosis '[1], when fully developed lesions are found in the foetus or infant at birth—a term preferable to that of ' prenatal tuberculosis ' used by Whitman and Greene[33], as the latter includes also merely the demonstration of tubercle bacilli in the placenta or organs of the foetus or infant; or (2) as ' congenital latent tuberculosis,' the possibility of which was first suggested by Baumgarten[2]. He considered that some tubercle bacilli were transmitted to the infant, in whom they lay dormant for a while, but eventually produced tuberculous disease. The delay in the development of the lesions he attributed to inherited resistance from the mother. Landouzy[21], on the other hand, suggested that the latent interval might be due to the small number of bacilli. When referring to the transmission of tubercle bacilli only the mother is generally considered, but it has been suggested by Baumgarten[2] that this might also occur through the male sperm. The description of a filterable form of the tubercle virus (Fontès[14], Vaudremer[32], Valtis[31]), and the reported demonstration of its passage from a pregnant guinea-pig to the foetus (Calmette, Valtis, Nègre, and Boquet[6]) introduces a further possibility as regards the transmission of the ' seed ' both from the mother and the father.

Inheritance of soil includes the possibility of transmission of toxins and antibodies from the mother to the foetus, generally considered under this heading. [This classification is perhaps not accurate, although both these substances might influence the growth of tubercle bacilli acquired after birth.] Also to be considered is the inheritance of certain cellular

* Part of a report on work done while holding a Dorothy Temple Cross Research Fellowship in Tuberculosis awarded by the Medical Research Council.

characteristics or a ' diathesis.' The following effects have been stated to result from these factors: a. various constitutional effects, such as still-births, congenital deformities, ' tuberculous type,' and many other conditions (Landouzy[21] and Mosny[24]); and b. a predisposition to the development of tuberculous disease, the organisms having been acquired after birth (Hutinel[18], Diehl and v. Verschuer[12], Ickert and Benze[19]).

Evident congenital tuberculosis.

The occurrence of tuberculous lesions in the newly-born infant is known as a rare phenomenon. The infant is either premature, still-born or dies shortly after birth. In the last case it may be difficult to exclude the possibility of post-natal contagion unless the infant has been rigidly separated from the mother immediately after birth (see Couverlaire and Lacomme[8]). Whitman and Greene[33] reported a case of evident congenital tuberculosis and reviewed the literature on the subject. Couvelaire and Lacomme[8] found one example in a successive series of 500 tuberculous women who were confined in the special department of the Baudelocque Maternity, although it is to be noted that only 66 of the 116 infants who died in the first three months died at Beaudelocque (the diagnosis in the remaining 50 is not stated); in another case the possibility of post-natal contact could not be excluded. Lelong[22] describes evident congenital tuberculosis as presenting three types of pathological picture. The main feature in all is that the lesions are not predominantly pulmonary. On the other hand, Habitz[16] reported a case of ' congenital tuberculous infection with certainty ' dying at three weeks, the same day as the mother, and at the post-mortem examination disseminated tubercles were found in both lungs of the infant. For fuller details and references on the subject of evident congenital tuberculosis reference should be made to the papers of Whitman and Greene[33], Debré and Lelong[10], and particularly Siegel[30].

Mechanism of transmission of the tubercle virus.

Clinical observation as shown by the occurrence of evident congenital tuberculosis has thus established that the transmission of the organisms of tuberculosis may occur. The view that tubercle bacilli may be transmitted by the spermatozoa or the ovum has not received much support. The presence of tubercle bacilli in either of these germinal cells has never been satisfactorily demonstrated and it seems probable that an ovum so infected would not be likely to mature. Friedmann[15] has described animal experiments suggesting the possibility of such transmission. The filterable form of tubercle virus appears to offer a further possibility in this direction. The amniotic fluid is not likely to play the sole part in the transmission,

A rare phenomenon may be the passage of tubercle bacilli to the placenta as the result of extension from tuberculous lesions of the genital tract of the mother. Transplacental transmission seems the most likely mechanism. It is of interest to mention the observation of Debré and Lelong[10] that all published cases of evident congenital tuberculosis are concerned with foetuses more than four months old, the period when the placental circulation is established. It is probable, however, that earlier foetuses are rarely obtained and examined.

Work along various lines tends to support the theory of transplacental transmission of the tubercle virus.

(1) The presence of tubercle bacilli in the blood of tuberculous patients under certain conditions has of recent years been demonstrated.

(2) Tuberculosis of the placenta has been described. Debré and Lelong[10] quote the work of Schmorl, Lehmann and Sitzenfrey. While admitting the rarity of microscopic lesions in the placenta these German authors insist on the frequency of such lesions in tuberculous women (Schmorl 45 per cent., Lehmann 45 per cent., Sitzenfrey 27 per cent.). These lesions may occur as extension of uterine tuberculosis but most commonly as the result of spread through the blood. They are rare in chronic pulmonary tuberculosis. Debré and Lelong[10] themselves examined the placenta of twenty-eight tuberculous women. No macroscopic lesions were discovered in any of them, and guinea-pig inoculations remained negative. It may be asked, whether or not a healthy placenta allows the passage of tubercle bacilli. Debré and Lelong[10] quote evidence that maternal white blood corpuscles may pass into the placenta. It may therefore be assumed that tubercle bacilli could be carried by these cells or passed through on their own, ' the fact that the bacilli are present in the placenta is not necessarily proof of their reaching the foetus.' Debré and Lelong injected into guinea-pigs 5 c.c. of the blood from the umbilical cord of the babies of ten tuberculous women. All the results were negative.

(3) The filterable form of the tubercle virus (ultra-virus tuberculeux) was first described by Fontès[11], of Rio de Janeiro, in 1910. His discovery was at first discredited but observations similar to his were made by Vaudremer[32] in France in 1922. The subject was then further investigated by Valtis[31] and bacteriologists in several countries. The organism is described as a Chamberland filter-passer, non-acid-fast, capable after repeated animal passages of giving rise to an acid-fast bacillary form. Calmette, Valtis, Nègre and Boquet[6] demonstrated the passage of this filterable virus from pregnant guinea-pigs to the foetus. Calmette, Couvelaire, Valtis, and Lacomme in the experiments described below demonstrated the presence of the filterable virus in the organs of the foetuses or infants dying soon after birth. It must be stated that considerable doubt is widely expressed as

regards the existence of this virus. It is felt that the results are due to the passage of a few bacilli of little virulence through the filter.

(4) The presence of tubercle bacilli in infants dying from general causes. Debré and Lelong[10] performed careful necropsies with aseptic precautions on fifteen infants born of tuberculous mothers (all of whom had bacilli in the sputum but varied in the degree of severity of their disease—from ' most benign forms to very severe, several dying soon after the confinement '). These infants were born dead or died soon after birth from unknown causes. Histological examinations and guinea-pig inoculations from numerous organs and placentas were carried out with negative results. On the other hand, Couvelaire and Lacomme[8], with the help of Calmette, performed experiments along similar lines with the organs of twenty-six foetuses and infants still born or dying soon after birth from tuberculous mothers suffering chiefly from advanced disease, and found in twenty infants either typical tubercle bacilli or a filter-passer. For fuller details of these experiments and discussion of results see Calmette and Valtis[5]. (See also the conclusions of Couvelaire and Lacomme[8] on the result of these and other experiments with the filterable virus.)

Inheritance of soil.

Transmission of toxins. Debré and Lelong[10] examined the organs, and particularly the liver and spleen, of still-born infants or those separated from their mother at birth, for histological changes suggesting toxic lesions. Their results were negative. Similarly Couvelaire and Lacomme[8] mention that in their experiments with twenty-six foetuses and infants already quoted no evidence of any toxins could be discovered in the filtrates of the organs.

Transmission of antibodies. The transmission of antibodies from mother to foetus is known to occur in relation to diphtheria and measles. In regard to tuberculosis, antibodies were first demonstrated in the human foetus by Parisot and Hanns[26] using the Bordet-Gengou complement-reaction, and later by Rosencranz[29]. The work of Ribadau-Dumas, Cuel, and Prieur[28], Cooke[7], and Debré and Lelong[10] shows that (1) the passage of antibodies for tuberculosis from mother to infant via the placenta is a definite and frequent phenomenon; (2) that it is not simple filtration, for the placenta seems to take an active part in concentrating or activating them; and (3) that the antibodies rapidly and spontaneously disappear in eight to ten weeks.

Clinical observations on 500 tuberculous mothers. The observations of Couvelaire and Lacomme[8] on a consecutive series of 500 confinements at a special department for tuberculous women at the Baudelocque Clinic were made under unique conditions and their findings will be briefly summarized. The women were observed over the period 1921-1927. In almost all the cases bacilli were present in the sputum. In the remainder the diagnosis was confirmed by a competent physician. A few suffered from non-pulmonary tuberculosis. All infants born alive were separated from the mothers immediately at birth, and stayed at the hospital on an average from one to two months. Afterwards they were in most cases separated, being either brought up by relatives away from the mother or else sent to ' L'Oeuvre du Placement Familial des Tout-Petits,' an association which boards out these

infants and home-contacts with healthy families in the country under medical and nursing supervision. It will be referred to subsequently as the ' P.F.T.P.' No abnormal intrauterine development was noted. There were eleven abortions. With weight as a criterion, prematurity was relatively infrequent. The weight of the infants at birth was in the majority of cases under the average of new-born in the hospital class. Death of the foetus in utero with retention and maceration was observed in only three cases. The appearance of all the other infants at birth was normal. Malformations were rare. Thirty-four were still-born; these include infants dying in the first three days, according to the custom of official statistics in France. (In France a delay of three days is allowed in registering a birth. An infant who was therefore not registered and died within that period may be notified as still-born.)

The relation between physical state of new-born and tuberculosis of mother is of interest. In regard to malformations, these were too few for the relation to have any value. A direct relation was however found between the severity of the mother's illness and the abortions and weight of the infant at birth.

TABLE 1.

Of 51	mothers who aborted or gave birth to infants	under 2000 gm.	33	or 64·7	per cent.	died	within	three	months	
Of 62	mothers who gave birth to infants	weighing 2000-2500 gm.	33	,, 53·2	,,	,,	,,	,,	,,	
Of 153	,,	,, 2500-3000 ,,	70	,, 44·7	,,	,,	,,	,,	,,	
Of 152	,,	,, 3000-3500 ,,	37	,, 24·4	,,	,,	,,	,,	,,	
Of 66	,,	,, 3500-4000 ,,	7	,, 10·6	,,	,,	,,	,,	,,	
Of 16	,,	,, over 4000 ,,	0		,,	,,	,,	,,	,,	

This direct relation does not necessarily imply a specific relation; the explanation may merely be that the tuberculous toxaemia causes prematurity as in any acute illness or infection.

The authors' conclusions on the total deaths (up to three days of life and including abortions) from the 500 women are as follows:—The total of fifty deaths (it is difficult to see how this figure is arrived at as eleven abortions and thirty-four still-births make a total of forty-five only), includes eight syphilitics, four due to obstetrical trauma and two abortions definitely not due to tuberculosis, leaving a total of thirty-six foetuses and new-born infants whose death might be attributed or indirectly to tuberculosis, giving an ' initial mortality ' of 7·2 per cent.

There were 450 living infants from the 500 tuberculous women. Most of them stayed at Baudelocque a few weeks, many three months and some more than four months. Amongst them 116 or 25·7 per cent. died before the age of three months (61 died in the first month). Of these, 66 died at Baudelocque (this number includes two who died in the fourth month); forty-six of them were premature or weighed less than 3,000 gm.

The causes of death are divided into (a) infections (pulmonary, otitis, influenza, erysipelas), 41; (b) various causes such as strangulated hernia, convulsions, etc., 8; (c) tuberculosis, 2 (see page 158); and (d) progressive malnutrition, 15. Three-quarters of (a) and (b) are attributed to cross-infection (as shown by the fact that groups of death occur periodically) and to artificial feeding. Improving the hygienic conditions of the wards by prompt isolation of sick infants and introducing human milk fo feeding

caused an immediate drop in this mortality. The term progressive malnutrition is applied to a group of infants who, weighing slightly less than average at birth, continued to lose weight after the normal initial fall and died at the end of the first to the third week without clinical or post-mortem signs of any lesion. These deaths occurred even when the infants were fed on human milk. A similar syndrome was found amongst infants of mothers suffering from other severe illnesses, but more rarely. The syndrome has apparently no relation to the gravity of the tuberculous disease in the mother. Moreover, this mortality diminishes as the conditions of the rearing of the infants improved. Thus there were ten deaths in the first series of 209 and five deaths in the second series of 241, but it does not disappear entirely. Lelong[22] considered that it was due entirely to the artificial conditions of upbringing, but Couvelaire and Lacomme did not find this syndrome amongst infants of healthy mothers under similar conditions. They attributed it to the tuberculosis of the mother. The successive drop in the mortality of the infants from tuberculous mothers at Baudelocque is shown in the follows:—Third day to third month, 116; third to sixth month, 30; sixth from third day; see page 161).

TABLE 2.

Year.	No. of cases.	Deaths.	Mortality per cent.
1921-23	57	19	33
1923-25	151	20	13·2
1925-26	111	8	7·2
1926-27	131	14	10·7

The progress at Baudelocque of most of the infants who survived was that of normal infants. In some there was a difficulty with feeding, the gain in weight at first being irregular. A third group behaved at first like the group described under progressive malnutrition, then suddenly without change of diet, they began to put on weight, as if they had ' overcome something.'

Later mortality. Of the surviving 450 infants 184 were dead at the age of three years (mortality 40 per cent.). These deaths were distributed as follows:—Third day to third month, 116; third to sixth months, 30; sixth month to a year, 26; one to two years, 9; two to three years, 3. Of 112 infants taken away by the relatives 24 died before three months and 44 later, giving a total mortality of 60 per cent. up to three years. Of the 184 deaths, 66 occurred at Baudelocque—64 before three months, and 43 at the P.F.T.P. —13 before three months (it is stated that none of the latter died of tuberculosis). This leaves a total of 75 deaths out of 184 (40 per cent.) which occurred in the family or in other hospitals. Of the 116 who died under three months 66 per cent. had been under observation either at Baudelocque or at the P.F.T.P. The diagnosis in the 75 infants whose death occurred outside these two institutions is not stated.

The main criticism of the paper by Couvelaire and Lacomme is that nothing is said with regard to the infants who died in the first three months elsewhere than at the Baudelocque Clinic and the P.F.T.P. The argument that as ' most of these infants had often been in more or less prolonged contact with their tuberculous mothers ' which ' would suffice to remove all interest from the diagnosis even if it could be known,' does not disprove that some of them were possibly examples of evident congenital tuberculosis. Similarly nothing is said with regard to the cause of death of the older children who did not die at the P.F.T.P. In these again it is not known in what rôle contact played and they might include examples of congenital latent tuberculosis.

Whilst the investigation is thus incomplete, nevertheless the occurrence of only one case of evident congenital tuberculosis and of no case of tuberculosis up to three years in the children under observation (more than half of the total number, and not a picked sample) tends to support the conclusions of Couvelaire and Lacomme which are as follows:—(1) (Evident) congenital tuberculosis is exceptional. (2) Latent congenital tuberculosis does not show itself at any rate up to the age of three years in infants separated at birth. (3) The large infantile mortality in the first few months is chiefly due to the artificial upbringing, but a specific factor cannot be excluded.

Discussion.

The results obtained by separating infants and children from tuberculous parents as carried out by the existing associations in France need not be considered here, for, as will be shown below, they can neither prove nor disprove the possibility of latent congenital tuberculosis or of ' inheritance of the soil.' From the evidence submitted in this paper it seems impossible to form any definite conclusions as to the rôle of heredity in the causation of tuberculosis.

In discussing the ' inheritance of the seed ' of tuberculosis it is essential in the first place to distinguish sharply between children born of tuberculous fathers and those born of tuberculous mothers. It is extremely unlikely that transmission of organisms from the male occurs, unless the existence of the filterable form of the virus be definitely admitted. That transmission of bacilli from the mother occurs not infrequently seems probable. The existence of cases of evident congenital tuberculosis presupposes the possibility of the passage of small number of bacilli with a delay in the appearance of tuberculous disease. This is further supported by the finding of tubercle bacilli in still-born infants or in those dying shortly after birth after having been rigidly separated from their mothers. Moreover the filterable virus may play a rôle in view of the experiments quoted.

Unfortunately there is no investigation giving the causes of deaths of all the infants dying within even three months of separation from a large series of tuberculous mothers.

It might be argued that those infants who are most likely to inherit tubercle bacilli from their mothers would be born of women with advanced disease and acutely ill, and therefore would generally be under-weight and debilitated infants, likely to die in the first few days of their existence, before the tubercle bacilli have had time to produce definite lesions. The surviving infants would therefore (a) be less likely to have inherited bacilli and in any case in fewer numbers, (b) would be stronger, and (c) possibly be able to deal with the few bacilli by means of the antibodies which have been shown to exist in the infant in the first few weeks of life. The absence of tuberculosis in 217 infants separated at birth and brought up in a tuberculosis-free environment in the country by the P.F.T.P. may therefore be accounted for by selection, that is, they represent survivals who are not likely to have inherited any bacilli, or be due to the prevention of the development of tuberculous disease as a result of the improvement in the hygienic conditions. The latter reason has been brought forward by Lumière[23], a strong partisan of the theory of heredity.

In relation to the last argument it is essential to consider the question of tuberculin tests in the infants, separated at birth and brought up by the P.F.T.P., who did not have ' BCG ' (as the latter produces a positive tuberculin reaction after a varying interval). Bernard[3] states that with Debré he investigated the Pirquet test in 300 children from the P.F.T.P., separated from family contagion at birth or before infection has taken place (that is, they were Pirquet-negative on their admission) and ' placed in country homes absolutely free from tuberculosis.' Those children were excluded in whom the delay of the appearance of the reaction seemed too short to enable them ' to state definitely that the previous family contact, which had been interrupted, could not be incriminated.' Only five developed a positive Pirquet test during their stay in the country; in one of these contact had possibly taken place, but in the four others no contact whatever could be ascertained (three of these infants had been separated at birth).

A little later, however, Bernard, Debré, and Lelong[1] state ' en effet chez les enfants séparés dès la naissance et que nous avons longuement suivi dans les mêmes centres d'élevage, s'ils n'ont pas reçu de BCG, jamais la cuti-réaction ne s'est montrée positive.' Again, referring to the same children Debré and Corfino[9] state that these children maintain a negative Pirquet reaction till their departure (at four years) except in a few exceptional instances, where they have been able in each case to find visits of tuberculous parents and contacts. They state that of 151 such children they examined with the Mantoux test (up to a dilution of 1 in 200) all were negative. Debré, Lelong, and Pictet[11] tested eighty children (who had been separated at birth) with the Mantoux test up to a dilution of 1 in 10—all were negative; but amongst 134 children who had been in contact some time before separation, but were Pirquet-negative on admission (those who became positive soon

after admission are not included in this group, but are assumed to have been contaminated), twenty-one gave a feebly positive or doubtful reaction. It should be stated that contrary to the opinion expressed by Hart[17] that the frequent occurrence of false reactions with this dilution necessitated the use of a control test, these authors had not employed the latter in their investigation.

According to Léon Bernard's original statement one must assume that the environment of these children in the country is not ' absolutely ' free from tuberculosis; otherwise one is faced with the conclusion that the three children separated at birth who developed a positive Pirquet test may be cases of congenital latent tuberculous infection. It is of interest to note that of these three children one had a tuberculous father and the reaction became positive at the age of three-and-a-half years, and in the other two the mother was tuberculous, the test becoming positive at the age of one year and of two-years-and-eight months respectively. The long latent interval does not necessarily exclude such a possibility for the following reasons. (a) It is considered by some authors that a period even up to four months (ante-allergic period) may elapse between the time of contact and the appearance of a positive tuberculin test. (This is not admitted by every worker, Wallgren (private communication), for example, considers the maximum as eight weeks.) It is possible that when tubercle bacilli are inherited, because of the small number in these surviving infants and because of the inherited immune bodies, such a latent period may be more prolonged. (b) The Pirquet test is admitted not to be very sensitive, and it is possible that if a Mantoux test in a strong dilution had been used these three infants would have been found to react positively at a much earlier age. (c) The association between the filterable form of the tubercle virus and the state of allergy is not yet understood. A recent paper by Paisseau, Valtis and van Deinse[25] describes positive skin tests obtained with a tuberculin derived from the filterable virus in the absence of a positive test with ordinary tuberculin. It must be concluded that even at the estimate of three positive Pirquet reactions in an environment assumed absolutely tuberculosis-free, the presence of latent congenital tuberculous infection is rare.

If it is assumed that the transmission of bacilli from the mother to the infant may rarely show itself as a positive tuberculin test after an interval of a year or more, must the appearance of tuberculous disease in these children be expected after a short interval? This is not necessarily so. It is considered by many authorities that pulmonary tuberculosis in the adult is at any rate in many individuals the result of endogenous reinfection from tuberculosis acquired in childhood, that is, there exists a latent period of some years. It is reasonable to assume that such a prolonged latent period may occur between the appearance of a positive tuberculin test due to inherited bacilli and that of manifest disease, which may thus show itself only in adolescence. Only the fate of a large number of children separated from all tuberculous contact since birth and followed up to adolescence could

decide this point and it might well be asked whether an absolutely tuberculosis-free atmosphere could easily be obtained for this length of time. The statistics offered by the P.F.T.P. do not help, for this association only has existed since 1920, keeps children only till the age of four years, and, in any case, soon after its foundation it became the practice to vaccinate the children with BCG. Similarly, the results of the Oeuvre Grancher, although founded in 1903, are useless, as (a) until 1920 only children from the age of three years were admitted, most of whom are already infected and picked as regards their good health, (b) the Great War interfered with the following-up of those under the care of the association before 1914, (c) no adequate follow-up department exists at present, and (d) a large proportion of the children are taken out by their parents after only a short stay.

Inheritance of the soil may be regarded as a diathesis favourable to the development of the tubercle bacillus and transmitted along Mendelian lines. So that while heredity would not determine infection, it would in some individuals (children or adults) determine the development of disease once infection has been acquired as the result of contact after birth. Karl Pearson[27] after statistical analysis of 383 patients in whom the family history was exhaustively studied states ' the diathesis of pulmonary tuberculosis is certainly inherited, and the intensity of the inheritance is sensibly the same as that of any normal physical characteristic, for example, stature, span, cubit, eye-colour, etc., yet investigated in man. A theory of infection does not account for the facts.'

The most serious contribution to this subject of recent years is the work of Diehl and v. Verschuer[12] who elaborately examined (including the family history and environment) 126 pairs of twins in 106 of whom at least one of the pair had some tuberculous manifestation. They found that whereas ' tuberculosis concordance ' was present in 70 per cent. of the uniovular twins it was only present in 25 per cent. of the binovular. They conclude that a hereditary specific predisposition (i.e. involving morphological and immunological characters) exists, and that its influence becomes more marked with age. Ickert and Benze[19] after analysis of the genealogical trees of eighty-eight families reach the same conclusion and suggest that it is transmitted as a recessive character. On the other hand, Drolet[13] found that adult consumptives born of tuberculous parents resisted the disease better. His work has, however, been severely criticized.

The follow-up department of the P.F.T.P. has not yet been able to collect evidence to indicate whether such a diathesis may play a part in determining tuberculous disease in home-contacts already infected. But a considerable number of the children admitted with a positive Pirquet test and separated, after careful observation to insure that they are not clinically tuberculous at the time of admission, developed tuberculous disease later. With regard to the Oeuvre Grancher, Armand-Delille[1] gives the following

figures: 4,000 children admitted since 1907, twelve cases of tuberculosis, with three deaths; but it must be remembered that by far the larger proportion of children leave after a short stay only and it is not known what happened to them.

Conclusions.

(1) The transmission of tubercle bacilli from mother to foetus occurs not infrequently, as shown by cases of evident congenital tuberculosis and the presence of tubercle bacilli in infants separated from their tuberculous mothers from birth and dying of other causes.

(2) Infants with inherited tubercle bacilli probably die in the first few days or weeks of life of (apparently) non-tuberculous causes.

(3) There is no evidence that heredity plays any rôle in the causation of the large incidence of tuberculous infection found amongst home-contacts.

(4) Heredity does not appear to be responsible for the occurrence of tuberculous disease in the children of tuberculous parents at any rate in their first few years of life, provided post-natal contact has been avoided.

(5) Inheritance of a diathesis or a ' specific predisposition ' may determine the occurrence of tuberculous disease and its prognosis, both in children and adults, once post-natal infection has taken place.

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A STATISTICAL STUDY OF NOCTURNAL ENURESIS

BY

ROBINA S. ADDIS.

Bed-wetting is a common and troublesome problem which faces many who have the care of children. No cure seems specific and there are many theories current as to its causation and consequently the treatment required. Accordingly it should be profitable to enquire more exactly into the symptom. It seems the time to abandon mere generalizations and to present actual figures. This study is confined to simple factual data capable of statistical analysis and psychological findings (which it is hoped to publish elsewhere) have been omitted. At the end of 1933 the Child Guidance Council (founded in 1927) appointed a psychiatric social worker to carry out research on enuresis for one year. Material was obtained from the case records of six Child Guidance Clinics in London. The research work was under the direction of a committee consisting of Drs. Mildred Creak, R. D. Gillespie, Emanuel Miller and William Moodie. It was decided to go through a section of the records to pick out the enuretic children and then compare them with the remaining non-enuretics in different ways. The year 1932 was chosen (the last completed year before the research began) and all the 1,705 new cases which attended during that year at the six clinics were carefully studied. Bed-wetting is so much a routine question in Child Guidance Clinics that it was safe to assume that the symptom if present would be recorded and division into the two groups was valid. Not only those referred for bed-wetting but all who wet the bed were classed as enuretic. The cases had already been selected by the mere fact of having been referred to a clinic which is for difficult or nervous children, but this applies to both groups so that they can safely be compared with each other.

Full psychiatric clinic records have been kept for so few years that all the tables in which time is a factor (e.g. age, place in family) must be conditioned by this fact. It cannot be questioned why elder brothers and sisters or parents were not sent to the clinic, nor why the child himself did not come much earlier because the treatment simply was not available. All that can be said in this enquiry is that conditions are the same for the non-enuretics as for the enuretics, but one group may be affected more than the other. The future will bring the required knowledge and there is rapidly increasing material as the work of the clinics extends yearly.

Accordingly this work is perforce preliminary. The results offered are intended to stimulate interest in the problem and to suggest lines for further

research. Intensive study of cases of enuresis provides such a net-work of possible factors that it is salutary to make an extensive survey submitted to the discipline of figures. The following results are founded on figures from the total new cases (1,705) in 1932 at the six Child Guidance clinics. All figures are worked out to the first decimal place.

Incidence of enuresis.

Enuretics as a percentage of the total cases at each clinic give the following figures:—

Clinics	I	II	III	IV	V	VI	Average
Percentage of enuretics	17·1	18·7	14·4	22·5	18·9	16·8	18·4

These differences are not significant and may be accounted for by domestic reasons. At clinic IV some research was being undertaken in enuresis and the consequent inquiries may have led to other bed-wetting cases being referred, i.e. institutions and families finding the symptom considered of interest in one patient might bring up others for the same reason. Clinic III was in its first year and had fewer cases than the others so that its percentage is less reliable.

The total of 18·4 per cent. probably considerably under-estimates the incidence of enuresis among the general child population, since there are many other treatments (including the traditional chastisement) offered besides psychiatry.

Sex incidence.

1. Differences between the clinics.—The expected proportions between boys and girls if there were no sex differentiation in enuresis have been compared with the actual figures for enuretics and non-enuretics at the six clinics (see fig. 1). The results show that in clinics IV and VI there are

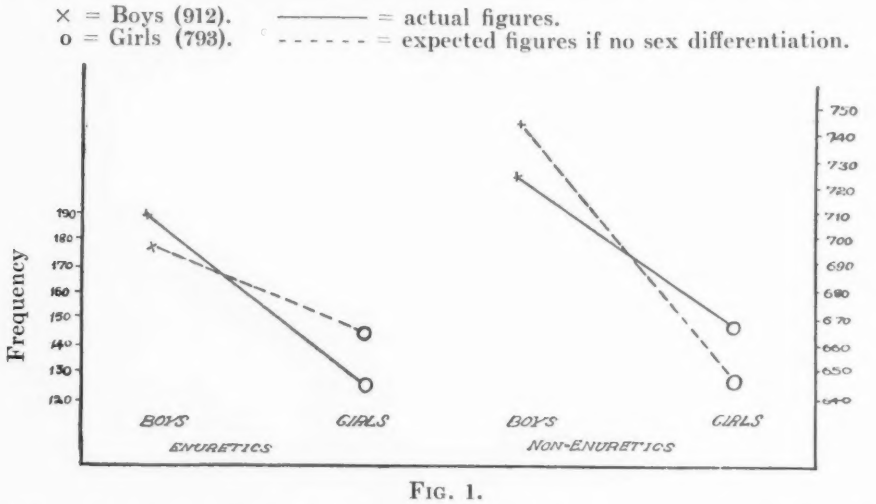

FIG. 1.

significantly more enuretics among the boys than among the girls. In the remaining four clinics the differences are not significant. (In III and V the excess is still among the boys but in I and II the proportion of the girls is slightly higher.)

2. Combined clinics.—If all the clinics are combined the findings are as follows:—

		Boys.	Girls.	Total.
Enuretics	actual figures	189	125	314
	expected figures	168	146	
Non-enuretics	actual figures	723	668	1,391
	expected figures	744	647	
		912	793	1,705

There are more boys than girls in the clinic population but even allowing for that there is a higher proportion of enuretics among the boys than would be expected if there were no connection with sex. Putting it to the nearest tenth of a number, it may be said that the proportions of boys and girls are as follows: enuretics 3 : 2 and non-enuretics 2·2 : 2.

Intelligence quotients.

1. Differences between the clinics.—(a) Enuretics are not a sufficient number (total=225) to prove that the variation among the clinics about the mean (I.Q. 97) is more than a chance effect.

(b) Non-enuretics (total=982) show a difference which might be regarded as statistically significant, e.g. between the means I.Q. 90·4 and I.Q. 90·5 of clinics II and III and the mean I.Q. 100·8 of clinic V. (Probable reasons for this may be found in the different class of patient which each clinic tends to attract according to its locality and working conditions. Allowance must also be made for the personal factor in different workers giving the tests.) See fig. 2 and 3, and table 1.

Intelligence quotients at the six clinics.

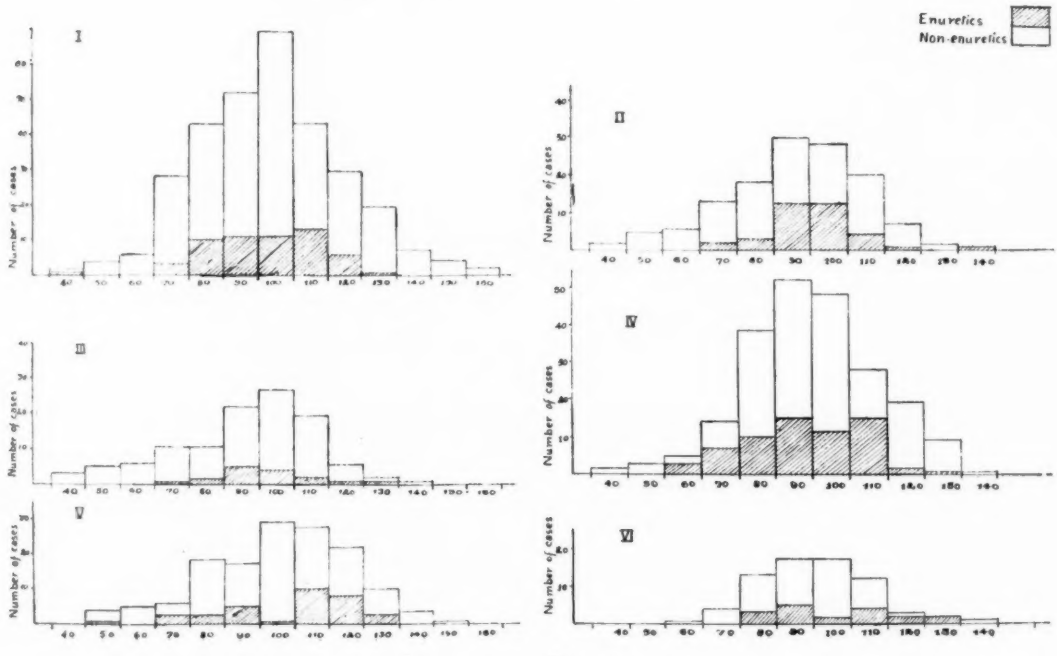

FIG. 2.

Chart shewing mean I.Q. for enuretic and non-enuretic children at six clinics.

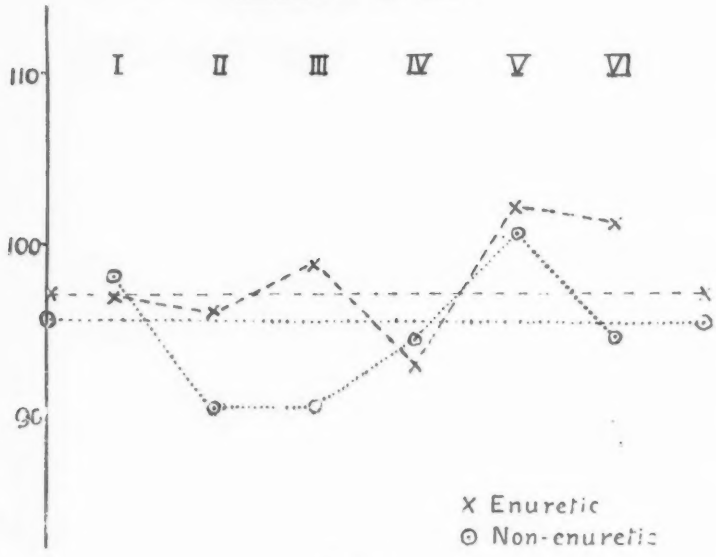

FIG. 3.

TABLE 1.

I.Q.	E.		Non-E.	
	Mean.	Standard deviation.	Mean.	Standard deviation.
Clinic I.	96·8	16·3	98·1	20·7
II.	96·0	12·8	90·4	18·4
III.	98·8	16·2	90·5	20·1
IV.	94·9	15·7	94·5	17·5
V.	102·9	19·7	100·8	20·5
VI.	101·7	15·8	94·6	14·1
Total	97·0	16·5	95·5	19·6

2. Combined clinics.—It seems justified to combine the clinics for the purpose of comparing the I.Qs. It is then found that the enuretics have a higher mean I.Q. (97·0) than the non-enuretics (95·5) but this difference is hardly big enough to have any significance. See table 1.

3. Variation.—(The variation of the individual I.Qs. about the average value is measured by the standard deviation.) In all the clinics, except clinic VI (with only 18 enuretics) the standard deviation for the non-enuretics is greater than for the enuretics. This characteristic is shown in the standard deviation of the combined clinics:—

Standard deviation for 982 non-enuretics = 19·6
Standard deviation for 225 enuretics = 16·5

Therefore the variation in I.Q. among the non-enuretics is significantly greater. This is due to the fact that they have a higher proportion of high I.Qs. and low I.Qs. but particularly the latter, considering the I.Qs. below 75 in more detail the following summarizes the findings:—

Enuretics = 21 out of 225 = 9·3 per cent.
Non-enuretics = 135 ,, ,, 982 = 13·7 per cent.

Diagram comparing I.Qs. of 225 enuretics with 982 non-enuretics = All cases with I.Q's. between 60 and 130.

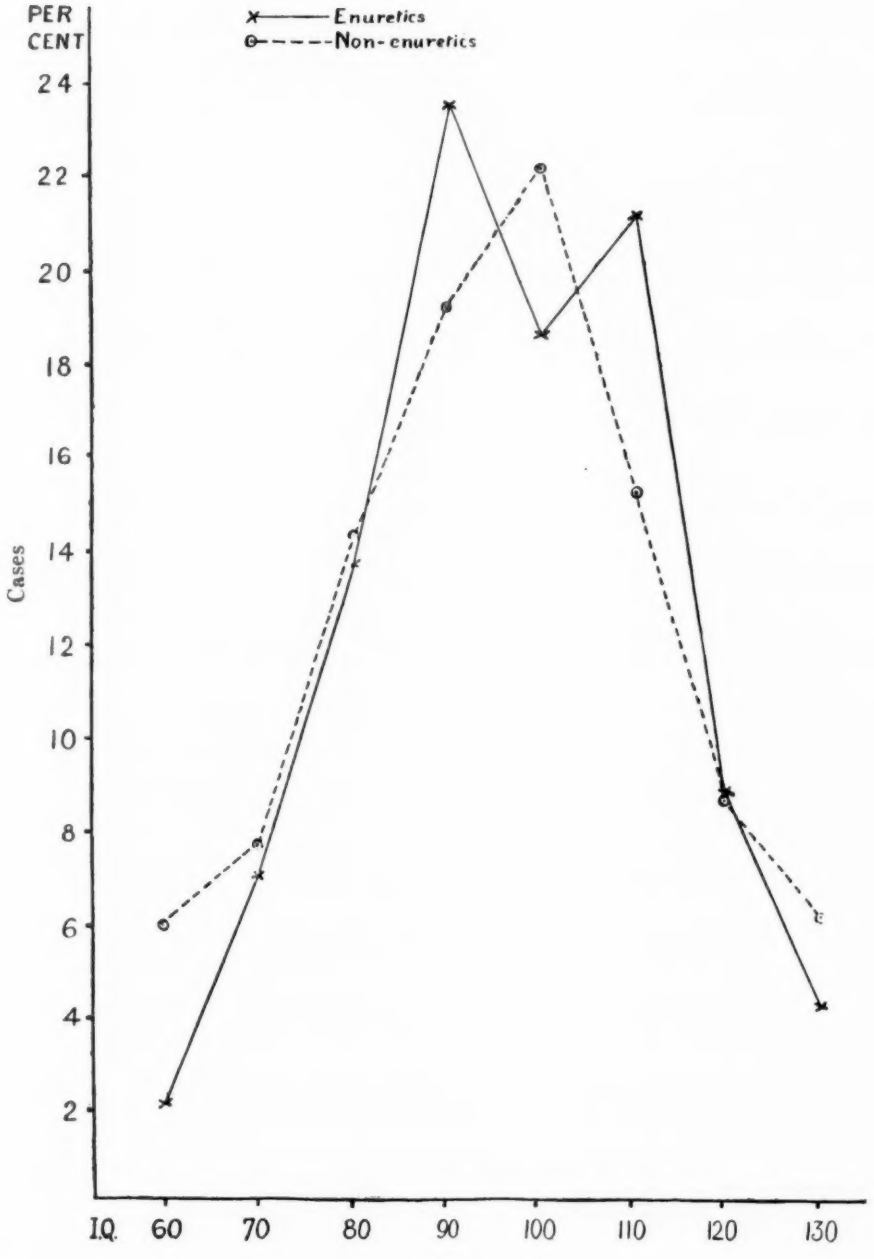

FIG. 4.

This difference is probably just significant. (N.B.—Although the clinics do not treat mental defectives some are sent for diagnosis and there are cases in which the defect has not been recognized as such but is accompanied by disorders for which treatment is asked. Thus indirectly cases are referred for mental defect and would be added to the list of non-enuretics if not

accompanied by bed-wetting). It is interesting to note that enuresis is not an invariable symptom where the I.Q. is low, e.g. at the idiot level:—

	I.Q. 40	I.Q. 50
Non-enuretics	10	22
Enuretics	1	1

4. Grouping.—I.Qs. have been grouped to the nearest ten (e.g. I.Qs. 95–104 are classed as I.Q. 100) and the six clinics combined to compare the enuretics with the non-enuretics. The number of cases in each I.Q. group was then taken as a percentage of the total cases to enable the groups to be drawn together (see fig. 4). Non-enuretics show the expected peak at I.Q. 100, but the enuretics have two peaks—at I.Q. 90 and I.Q. 110. Thus on the line of I.Q. 100 there is found a difference of 3·5 per cent. between the enuretics and the non-enuretics which is doubtfully significant with such a small number of the former. But the suggestion that there are two main groups of enuretics the one tending to dull and the other to superior intelligence may fit in with clinical pictures.

5. Conclusion.—There is no striking difference in I.Q. either between clinics or between enuretics and non-enuretics when the clinics are combined. The slightly higher I.Q. for the enuretics is probably due to the higher proportion of defectives among the non-enuretics, which is not surprising considering that some of these had come to the clinic for reasons associated with mental defect.

Age.

Children are taken at the clinics from a few months old to about eighteen years. In order to get large enough groups for comparison the clinics have been combined and the ages to the nearest year (e.g. one year and seven months to two years and six months, are classed as two years old) divided into broad groups correlated with school stages. (Since the actual ages are not given in this table and the groups are of different breadths, mean ages could not be calculated and compared. The number of enuretics in each year group would have been too small for statistical purposes.)

TABLE 2.

TOTAL FOR ALL CLINICS.

Years of age	Frequencies		Percentages	
	Enuretics	Non-enuretics	Enuretics	Non-enuretics
Below 5	29	18	9·3	8·3
5–7	63	228	20·2	16·7
8–10	113	387	36·2	28·2
11–14	85	447	27·2	32·6
Over 14	22	195	7·1	14·2
Total ...	312	1,370	100	100

It will be seen from these figures that for ages less than eleven years there are proportionally more enuretics than non-enuretics; for ages of eleven years and over the reverse is the case. Of the enuretics 65·7 per cent. come to the clinic while in the younger age group. This contrasts with the non-enuretics of whom only 53·2 per cent. are referred at under eleven years. The difference is large enough to be important. Enuretics are in fact significantly younger than the non-enuretics—which might support the popular belief that a child ' grows out of ' the symptom.

Place in the family.

1. Average size in family.—The following table gives the suggestion that enuretics come from families on the average about a third of a child larger than the non-enuretics.

Average size of family for enuretics	=	3·61
Average size of family for non-enuretics	=	3·27
Difference		0·34

Having regarded the variation about the average of observations, it can be said that the difference is just on the borderline of being significant.

2. Position in family as a percentage of total cases.—The children from families of different sizes may be combined and considered only in relation to their position in family. The following table gives the number of children in each place and the percentage of the total number of cases.

TABLE 3.

Position in family	Frequencies		Percentages	
	Enuretics	Non-enuretics	Enuretics	Non-enuretics
1st	116	588	41·6	47·8
2nd	72	283	25·8	22·0
3rd	42	160	15·1	13·0
4th	25	85	9·0	6·9
5th	12	40	4·3	3·3
6th and 7th ...	6	50	2·1	4·1
8th and 9th ...	6	23	2·1	1·9
—14th				
Total ...	279	1,229	100	100

These percentages do not show any marked difference between the enuretics and non-enuretics. It is not safe to draw conclusions from the marked preponderance of both groups in the position of first in the family, since ' first in a family of one child ' and ' first in a family of many children ' ought not to be classed together. The smaller the family the more likely it is that the child will be first and the only child is first for certain.

If only children are eliminated the following figures are obtained:—

Position in family	Total 671				Total 541			
	Families of 2 and 3				Families of 4 and more			
	Enuretic		Non-enuretic		Enuretic		Non-enuretic	
	Number	Per cent.	Number	Per cent.	Number	Per cent.	Number	Per cent.
First	54	46·2	276	49·8	18	15·3	60	14·2
Last	44	37·6	204	36·8	19	16·2	84	19·8
Other places	19	16·2	74	13·4	81	68·5	279	66·0
Total ...	117	100	554	100	118	100	423	100

These figures do not suggest any consistent factor relative to place in family as thus compared.

3. Average position in families of different sizes.—Figure 5 shows that in families of two, three and four, both enuretics and non-enuretics are close to the line drawn to show the average position were children coming to the clinic equally likely to be anywhere in the family. In families of five and over there is an increasing tendency for the position to be below the middle, i.e., later in the family than would be expected on a purely chance hypothesis. It cannot be concluded, however, that abnormal children in large families tend to be the later children, because conditions cause the material to be selected. If large families are in contact with the clinics, it must be the younger ones that are being treated, since the older ones are above clinic age. Position in family has been taken at the time of referral and the first or second children in small families may eventually be early children in large families. Satisfactory statistical results could be obtained only from comparing completed families (see fig. 5).

Diagram showing the average place in family of enuretics and non-enuretics in families of various sizes.

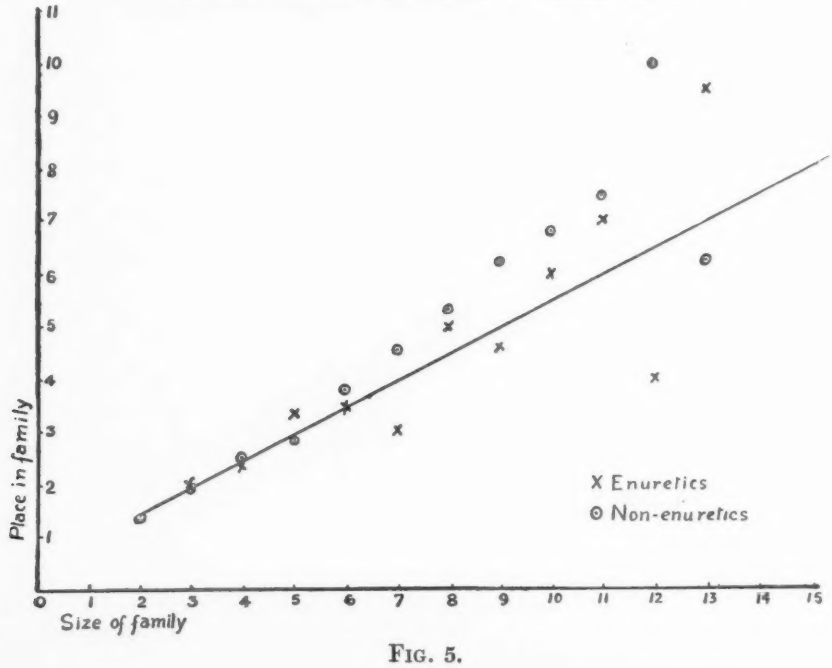

FIG. 5.

4. Comparison of position in families of the same size.—Figure 5 shows that the position of the enuretics is always a little earlier in the family than the non-enuretics in families of sizes six to twelve. For these seven types of families we find:—

	Enuretics	Non-enuretics
Average position in family ...	4·17	4·78

Whether this apparent difference has any meaning cannot be known from this one table (see fig. 5).

5. Only children.—

	Frequency	Percentage	
Enuretics	44	15·7	of Enuretics
Non-enuretics ...	259	20·5	of Non-enuretics
Total ...	296	19·6	of all cases

This difference is slight, but suggests that there are if anything rather a lower proportion of enuretics among only children than in families of two or more. Even if this were accepted there is too great a variety of possible psychological interpretations about the significance of being an only child to allow of any certain deductions.

Tentative deductions.

After this presentation of the statistics on their own merits, a few of the points which have arisen may be emphasized. Almost one out of every five children referred to the clinics for whatever reason, suffers from enuresis. This prevalence and its association with different sets of symptoms (which will be dealt with in the study of selected cases) suggests that enuresis is not an entity in itself but a symptom belonging to several conditions and brought about by varying mechanisms. That the proportion of boys to girls is 3 : 2 may be related to the difference between the male and female function of bladder control, or to less easily demonstrated causes.

An important result of the comparison of I.Qs. is the evidence that the enuretics fall into two groups of high and low normal intelligence. Clinical observation has shown two main types with lack of bladder control, the slow and lethargic and the restless and anxious. Endocrine as well as psychological findings can point to this division. Each type would call for special treatment and the importance of diagnosing to which group the child belongs is obvious. Another fact which may have far-reaching implications is that the enuretics had a smaller percentage of mental defectives than the non-enuretics. This is dependent to a certain extent on clinic conditions, but the striking fact remains that there were thirty-two children with I.Qs. of 40 and 50 who were not enuretic. This shows that enuresis is by no means an invariable symptom of feeble-mindedness, not even on the idiot level. Besides suggesting that bladder control is not a function of the intelligence, necessarily deficient when intelligence is low (and therefore even idiots and

imbeciles should be trained), this points to the constitutional and psychological factors predominating in enuresis. These findings are of much significance for treatment.

Incidence at different ages may also throw light on the nature of the symptom. Whereas non-enuretics are referred in increasing numbers for each age group up to fourteen years, the enuretics show their peak at eight to ten years and then decrease. They are significantly younger than the other cases and several reasons may be suggested. The beginning of puberty may have a specific effect as well as bringing to an end the so-called latency period when sex play is often manifest. The proximity of the genital and urinary tracts must cause congestion of one to affect the other and many indications suggest that enuresis is often connected with a sex factor. Such facts as bed-wetting occurring during periods of phantasy, as on first going to bed, and the dramatic clearing up of cases sometimes seen when tension about sex matters is relieved, point to this connection.

These considerations reach into realms beyond statistics, but speculations about quality have been based on quantitative findings. The discipline of figures was necessary to shape the path of enquiry and the tables have suggested many lines for future research.

Thanks are due to all those who facilitated the work and especially to Prof. Egon Pearson for supervising the statistics and to Miss V. E. Buxton for the patient help in checking the figures.

GASTROMEGALY FROM ARTERIO-MESENTERIC COMPRESSION OF THE DUODENUM IN THE NEW-BORN

BY

REGINALD MILLER, M.D., F.R.C.P.,
Physician to St. Mary's and the Paddington Green Children's Hospitals, London;

AND

H. COURTNEY GAGE, L.R.C.P., M.R.C.S.,
Radiologist to St. Mary's Hospital, London.

In this paper it is proposed to produce evidence that certain cases of obstructive vomiting in the new-born, simulating examples of intrinsic duodenal stenosis or atresia, are instances of duodenal ileus from arterio-mesenteric compression and are amenable to medical treatment; and to urge that where, in this type of case, radiological or other examination shows that the duodenal obstruction is not complete, duodenal ileus should be suspected and brief trial made of the effect of gastric lavage, in the hope of obviating the extreme risk of an abdominal operation. In support of these contentions three cases are reported; and it should be noted that, unlike the rare cases of duodenal ileus hitherto recorded in the very young, the obstruction is not associated with a gross megaduodenum although the duodenum is definitely larger than normal.

Chronic duodenal ileus (arterio-mesenteric compression), now established as a comparatively rare condition in adults, is regarded as possessing two causative factors: first, the congenital anatomical factor, the compression of the duodenum by the root of the mesentery and the superior mesenteric artery, and secondly, the accessory factor of visceral distension or ptosis whereby the compression of the duodenum is increased. The congenital anatomical factor has had to be assumed, otherwise it would be difficult to see why all cases of visceral distension or ptosis should not show signs of duodenal obstruction. The importance of the congenital factor has been emphasised in the studies of chronic duodenal ileus in young children by the present writers[1, 2]; and it is still more evident in examples of the same condition in the new-born such as are described in the present communication. In all cases in the new-born, and in most of those seen in early childhood, the presence of an obstructive factor dating from birth can be clearly traced. Nevertheless, even in early life, the importance of the accessory factor must not be under-estimated. In babies this takes the form of a ' paralytic ' distension of the stomach, and this is responsible for the occurrence of the urgent vomiting of the

obstructive type. Further, its treatment by gastric lavage and dieting promptly relieves and allows satisfactory progress to be made, even though the congenital factor in the duodenal ileus can be shown still to be operating.

Previous literature.—Several points of interest emerge from a perusal of the previous literature. Of prime importance is the observation of surgeons dealing with adult cases of duodenal ileus, that there is frequently a history of vomiting and dyspepsia in childhood, and that these symptoms tend to pass off in late childhood or adolescence, to return in later life. In a study of the same conditions in young children[1, 2] the same tendency to spontaneous remission of symptoms in later childhood was noticed and it was claimed that the type of case then reported was that previously foretold by surgeons. But in the cases described in early childhood it was found that there was sometimes a history of severe vomiting in the first few weeks of life, giving rise in some instances to a suspicion of hypertrophic pyloric stenosis. The cases recorded in the present paper are doubtless the same as these, caught in the neonatal period. Thus, if the evidence is accepted, chronic duodenal ileus has now been recognised at all stages : in the new-born, in later infancy and early childhood, and in later middle age as the long period of freedom from symptoms passes off. The age at which examples of this condition will come under notice may be assumed to depend on the comparative severity of the congenital and accessory factors in its production.

Another point of more difficulty is found in the fact that the only examples of chronic duodenal ileus described hitherto by other authors in infants and young children have shown megaduodenum associated with the duodenal obstruction. In 1930 eight such cases between the ages of nine days and four-and-a-half years were collected from the literature[1]. In them the vomiting of bile was a conspicuous feature. In none of the patients personally observed, neonatal or at a later age, could the enlargement of the duodenum be reasonably classed as megaduodenum, nor has bilious vomiting been more than exceptional. It seems clear that congenital arterio-mesenteric compression can produce in very early life two groups of cases : one showing megaduodenum with bilious vomiting and presumably requiring surgical relief, and the other, described here, which hardly shows either of these features and appears amenable to medical treatment. It is not easy to explain the difference between the two groups. If the megaduodenum is really due to the obstruction and not merely an associated anatomical abnormality, it may be supposed that in the cases with megaduodenum the congenital and unalterable pressure on the duodenum is more severe than in the type of case described in the present paper.

Lastly, extrinsic duodenal obstruction in the new-born has been described as due to peritoneal folds or bands, and success has been claimed to follow division of such bands. Such cases are exceedingly

rare, and in some instances operation has failed to relieve the symptoms. It is therefore possible that in certain instances at least the bands were really associated with arterio-mesenteric compression.

In 1927 D. P. D. Wilkie[3] pointed out the occurrence of symptoms in childhood in his adult cases of chronic duodenal ileus, and in 1933 R. P. Rowlands[1] noticed the same sequence of events.

Important papers on intrinsic duodenal obstruction were written by E. Cautley[5] in 1919 and H. C. Cameron[6] in 1925. Both agree that atresia is much more common than stenosis. ' In the great majority the occlusion is complete or all but complete, and unless relieved by operation life it not prolonged beyond two or three weeks ' (Cameron). Bile is seen in the vomit in 80 to 90 per cent. of the cases, and the duodenum appears as a ' widely distended pouch.'

Bernheim-Karrer[7] was the first to describe arterio-mesenteric compression as an extrinsic cause of duodenal obstruction in an infant. In 1904 he recorded the case of an infant whose symptoms dated from birth and who died at the age of eight months. At post-mortem examination megaduodenum was found associated with chronic duodenal ileus. Other cases of the same sort, all with megaduodenum, have been reported by Frank[8] (two cases), Downes[9], Dubose[10], Jewesbury[11], Henske and Best[12], and Camera[13].

R. Jewesbury and Max Page[14] in 1922 reported two cases of duodenal obstruction by bands. Both were neonatal cases. Adhesions were found round the duodeno-jejunal flexure, binding the jejunum in its first two or three inches to peritoneum on the posterior abdominal wall. These were the first cases of this type to be cured by operation, but at the time of reporting the second case had relapsed and its condition was stated to be not good enough to warrant further laparotomy. Both these cases showed megaduodenum, as did the successful one reported in 1926 by T. T. Higgins and D. Paterson[15]. F. Braid[16] in 1933 recorded an interesting case in which vomiting dated from birth, necessitating bottle-feeding until the age of two-and-a-half years. At four-and-a-half years the abdomen was opened and peritoneal bands, thought to be obstructing the duodenum, were divided. Progress was unsatisfactory, and the author suspected later an associated arterio-mesenteric compression, unrecognized at the time of the operation.

Case records.

Three cases are reported. In the first a diagnosis of incomplete duodenal obstruction was reached, but the possibility of arterio-mesenteric compression was not considered nor was its presence recognized at operation : this unsuspected condition was revealed post-mortem. In the second and third cases, seen later, this condition was suspected, and the diagnosis was taken to be confirmed by the evidence afforded by radiological examination and the successful results of medical treatment.

Case 1. (previously recorded[2]).—B. S., female, aged five days, was admitted to Paddington Green Children's Hospital on November 21, 1931. From birth she had vomited everything, and twice the vomit had been black or brownish.

On admission on the fifth day, she was dehydrated and on being fed she squirmed about as if in discomfort until the stomach was emptied by a copious vomit. The vomit contained much mucus, but showed no colouration by bile. Irregular gastric peristalsis was observed,

but was rather obscured by the wriggling movements of the child. No pyloric tumour was felt.

X-ray examination by an opaque meal showed the presence of incomplete duodenal obstruction (see below).

On the seventh day the child was failing, and in the hope that the obstruction might be due to some condition such as a band that could be easily dealt with, the abdomen was opened. The stomach was found to be large, the pylorus normal, the duodenum large and the jejunum

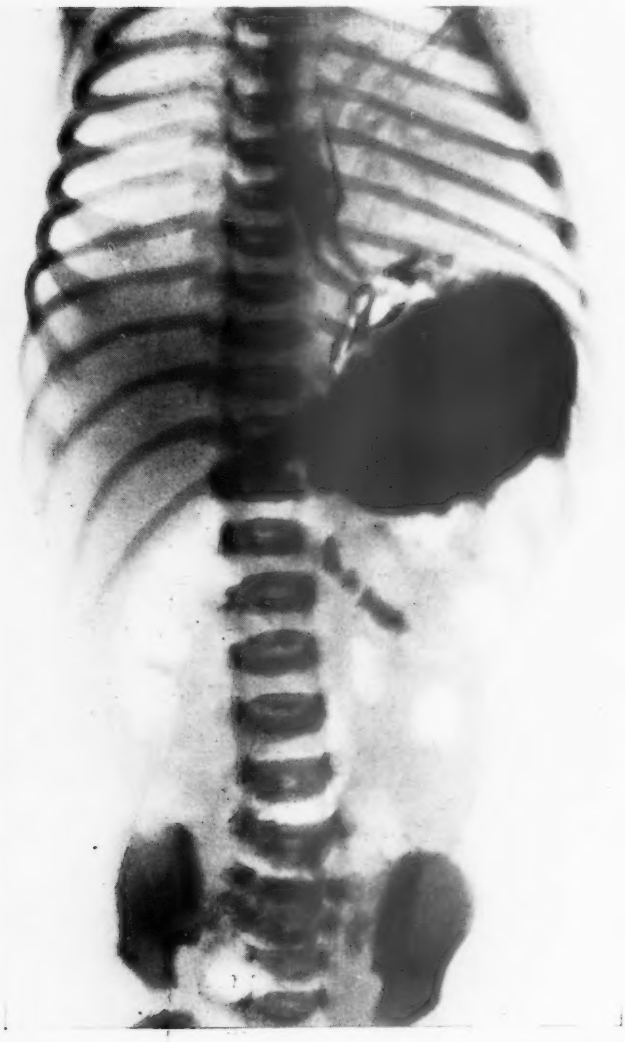

FIG. 1.—Case 1, aged 6 days; 1½ oz. opaque meal at 15 minutes, prone.

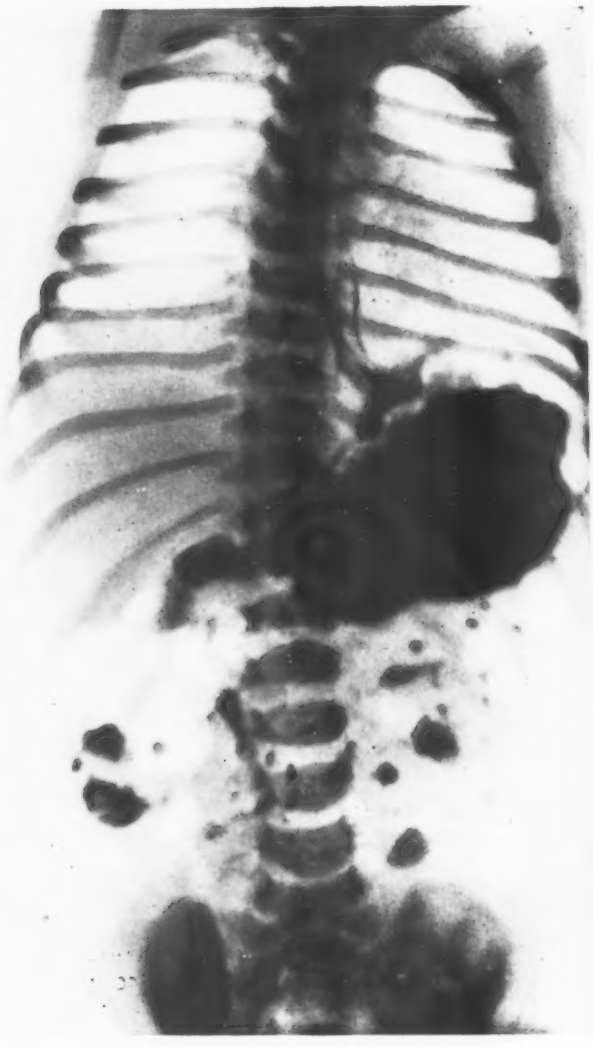

FIG. 2.—Case 1, aged 6 days; 1½ oz. opaque meal at 35 minutes, prone.

definitely narrow, but the cause of the duodenal obstruction was not localized. The infant died next day, aged eight days.

RADIOGRAPHIC EXAMINATION (November 21, 1935): One-and-a-half ounces of a fluid suspension of barium sulphate were introduced into the stomach by tube. On screening vigorous gastric peristaltic waves were seen.

The first film (fig. 1) was taken at fifteen minutes, prone. It shows a flocculent shadow of the barium, due to admixture with the contents of the stomach present before the meal was given. The outline of the

shadow is thus irregular and does not indicate in silhouette the true contour of the stomach, but only a puddle resting on the anterior gastric wall. It does not reach the fundus, nor does it fill the pyloric antrum as this passes to the right and backwards towards the duodenal cap. The stomach is therefore larger than the patch of barium at first sight suggests. The vigorous peristalsis seen on screening has already ceased although only a few minims of the meal have passed into the intestine,

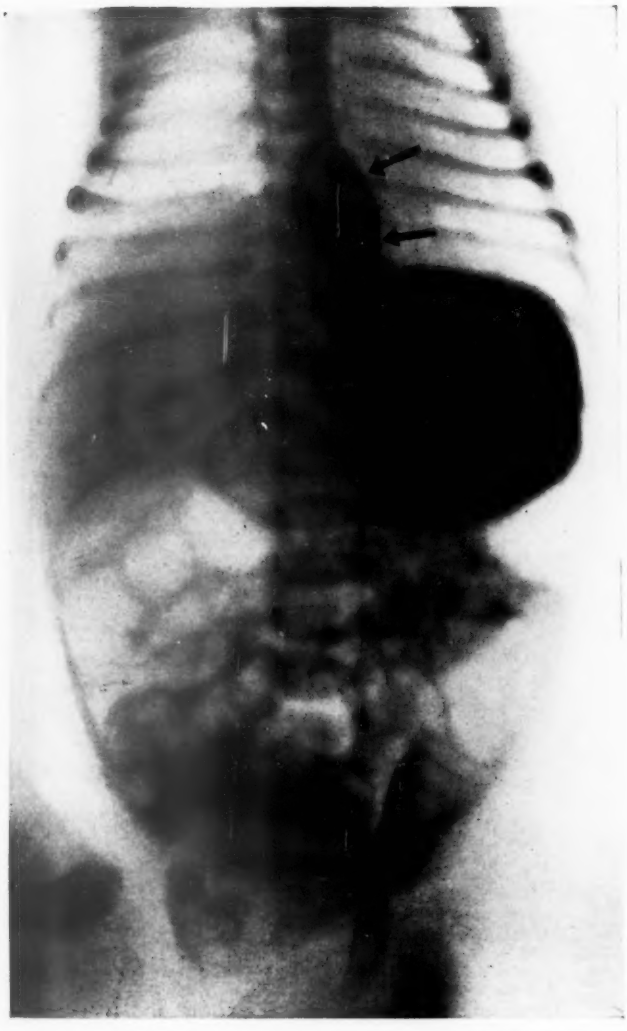

FIG. 3.—Case 2, aged 10 days; 1 oz. opaque meal at 20 minutes, supine.

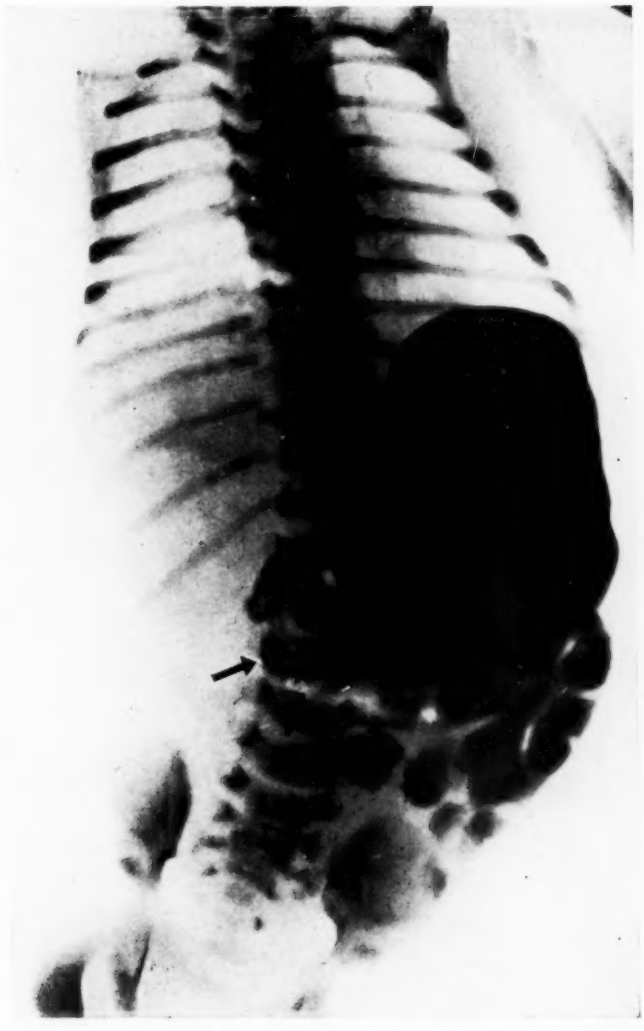

FIG. 4.—Case 2, aged 16 days; 2 oz. opaque meal on ingestion, supine

to be seen in the commencement of the jejunum as a narrow streak. No part of the duodenum is seen at this examination, but it is to be noted that the streak in the jejunum is at most not more than half the width of the part of the duodenum seen in fig. 2.

The second film (fig. 2) was taken at 35 minutes, prone. The general appearance of the stomach remains unchanged and only a few more minims of the meal have passed on, to be seen as flecks distributed

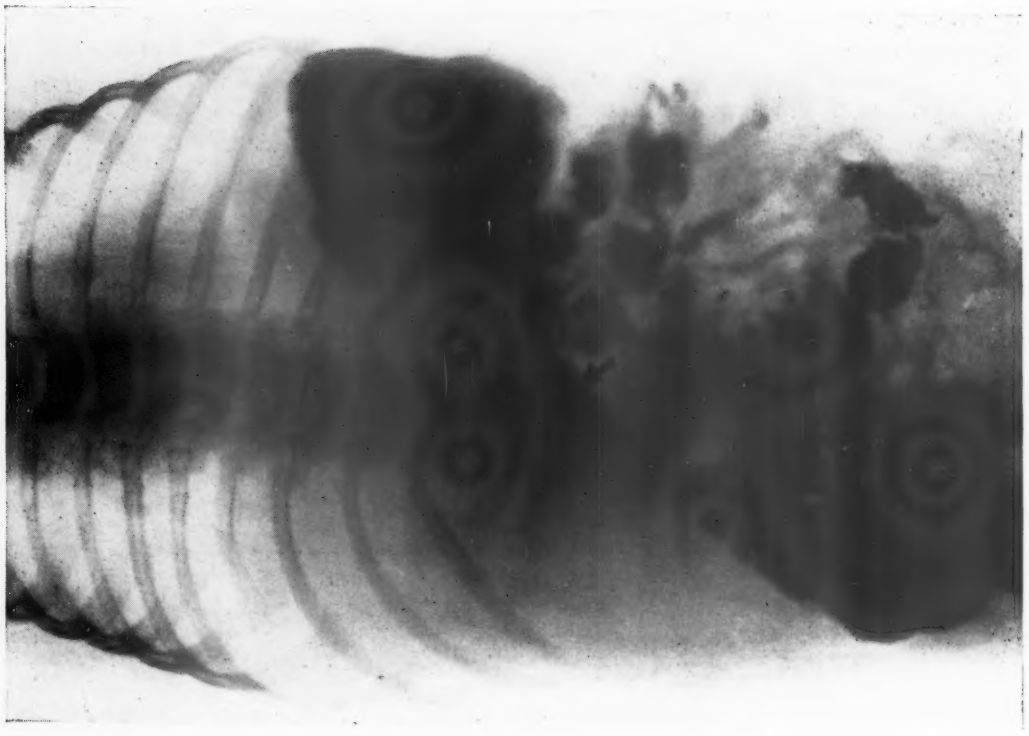

FIG. 6.—Case 2, aged 5 months; 7 oz. opaque meal at 2½ hours, prone.

FIG. 5.—Case 2, aged 5 months; 7 oz. opaque meal at 1 hour prone.

throughout the small intestine. This film, however, shows the duodenal cap and a small quantity of the meal in the second part of the duodenum.

The emptying time of the stomach was not taken, the presence of gastric delay being already established.

AUTOPSY.—The body of a small emaciated baby. When the abdomen was opened the stomach was seen to be moderately enlarged and the duodenum, also enlarged, was proportionate to the size of the stomach. Hypertrophy of the gastric wall could not be recognized with assurance.

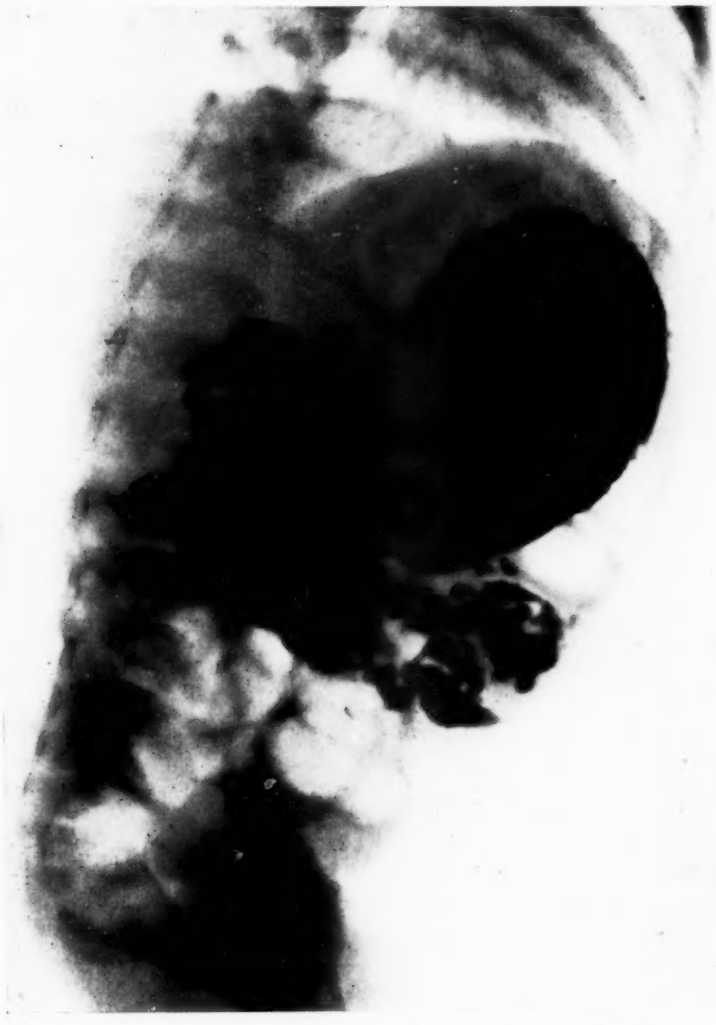

FIG. 7.—Case 3, aged 12 weeks; $4\frac{3}{4}$ oz. opaque meal on ingestion, oblique.

The jejunum was definitely smaller than the duodenum, between one-half and two-thirds of its width, and the change in the size of the gut came abruptly at the level of the crossing of the intestine by the root of mesentery and the superior mesenteric artery. The right kidney was completely absent. Except for the compression exercised on the duodenum, the disposition of the root of the mesentery and its vessels appeared normal.

Case 2.—A. F., female, aged ten days, was a first child, born at full term and admitted on May 18, 1934, with her mother to a private room at the Victoria Hospital for Children She was brought by Dr. H. Brade-Birks who stated that from the first the baby had seemed quite disinclined to take the breast. For the first two days she had vomited mucus, and from the third day she had vomited all breast-feeds. The vomits had been projectile, occurring about ten minutes after the feeds. No bile had been seen in the vomit at any time. It was thought that there had been a trace of milk-curd in the motion on the sixth day, but it was by no means certain that any food had passed into the intestine.

The baby on the tenth day was well nourished, but beginning to look ill. On being fed she squirmed about as if uncomfortable until the contents of the stomach were forcibly ejected. The stomach appeared large, but no peristalsis was seen nor tumour felt. The vomit contained much mucus but showed no colouration by bile.

In order to settle whether the obstruction were complete or not, an opaque meal was given without delay. This showed (fig. 3) that the obstruction was incomplete (see below), and in the hope that the case might be one of duodenal ileus the stomach was ordered to be washed out at once and again twelve hours later. The child had vomited the remains of the barium meal, but after the first wash-out all serious vomiting ceased. The first two wash-outs contained traces of bile.

The baby was seen next morning, May 19, in consultation with Mr. Jennings Marshall, and it was decided to continue the twelve-hourly lavage for a further twenty-four hours. At the end of this time progress was so satisfactory that it was agreed to continue with the lavage and four-hourly breast feeds.

On the sixteenth day, after six days of treatment, a second opaque meal was given. Radiographic examination showed that the stomach, although of more normal shape, was clearly enlarged and obstructed. Further, duodenal stasis was well demonstrated (fig. 4).

Gastric lavage was reduced to once daily and the baby progressed so well that she was sent home to continue treatment on May 29.

At five months she weighed 15¼ lb., and was progressing in every way satisfactorily. At this time (October 11, 1934) she was examined for the third time by an opaque meal. This showed conclusively that there was still present some obstructive factor which the vigour of peristalsis was overcoming satisfactorily (fig. 5 and 6). Gastric peristalsis was well seen clinically.

She continued to progress well, and remain symptomless. At ten-and-a-half months her weight was 22 lb. 1½ oz.

Radiographic examinations. (1) On May 18, 1934, the infant, aged ten days, was given one ounce of a fluid barium feed. Fig. 3 is from a film taken 20 minutes after ingestion, supine. It shows the lower oesophagus greatly dilated; the stomach much enlarged, ovoid, devoid of peristalsis, and protruding well over the region of the duodenal cap, which is consequently not seen. Very little food has escaped into the intestine. At 40 minutes the stomach and oesophagus were much the same, but a little more food had passed into the intestine. At 100 minutes the stomach was empty, the baby having vomited.

(2) After the stomach had been washed out twice daily for six days a second meal, consisting of two ounces of fluid barium was given on May 24, the baby being sixteen days old. Fig. 4 is from a film taken immediately after ingestion, supine. The stomach, although greatly enlarged, is more normal in shape than before, thus enabling the duodenal cap to be seen. A later portion of the duodenum is seen crossing the

vertebral column and exhibiting the classical cog-wheel formation of duodenal ileus. Much more food has passed into the intestine than at the first examination.

(3) On October 11, 1934, the baby, now aged five months and free of symptoms, was given a third opaque meal consisting of seven ounces of fluid barium. Fig. 5 is from a film taken at one hour, prone. The

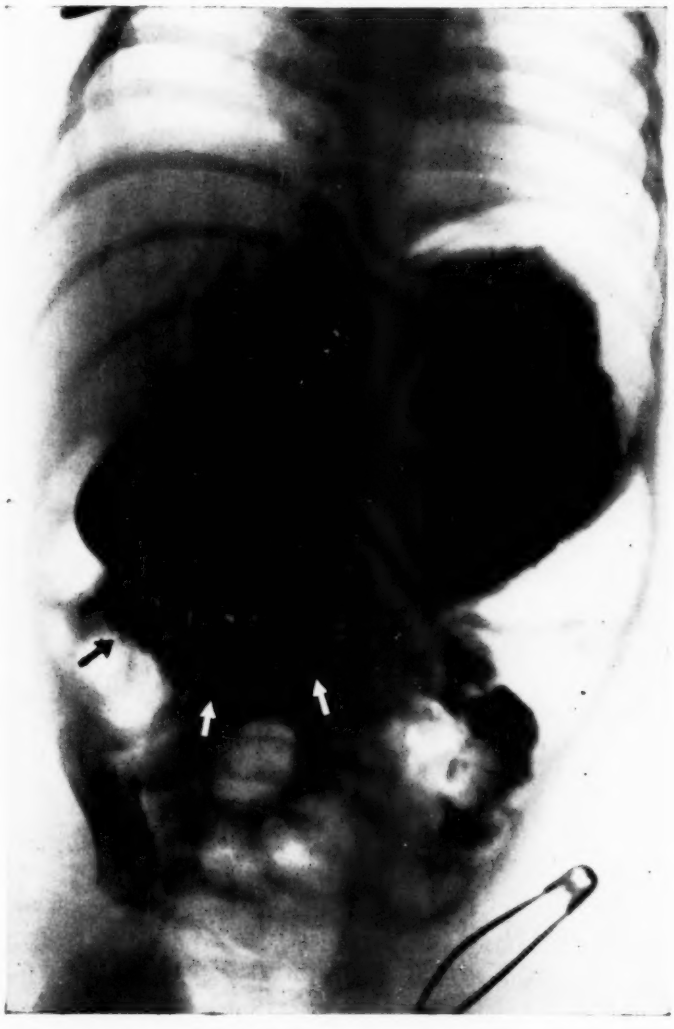

FIG. 8.—Case 3, aged 12 weeks; $4\frac{3}{4}$ oz. opaque meal on ingestion, prone. (The outline of the duodenum below the stomach has been artificially emphasised.)

stomach is very large and the barium is resting on the anterior wall of the stomach. The real outline of the stomach is seen to be larger than the shadow of the barium. Its wall exhibits obvious hypertrophy and hyper-peristalsis is clearly seen. Fig. 6 is from a film taken at $2\frac{1}{2}$ hours prone. The residue of the meal is in the fundal portion of the stomach, and the duodenum is seen crossing the vertebral column obliquely, indicating duodenal stasis.

Case 3.—A. G., female, born November 9, 1934, was a first child, full-term, weighing at birth 6¼ lb., and breast fed for six weeks. From birth until she was admitted to St. Mary's Hospital, aged eight weeks, she had been under continuous medical treatment, at first for vomiting and later for vomiting and diarrhoea. Vomiting started at birth, but it was not sufficient to prevent some gain in weight during the first three weeks. Then it gradually increased and became frequent, copious and projectile, and later was accompanied by diarrhoea. By December 27 she was so ill that she was admitted to another hospital from which she was removed on January 7, 1935, having lost one pound in weight. The next day she was admitted to St. Mary's Hospital.

On admission (January 8, 1935) she was eight weeks old and weighed 8 lb. She looked ill and dehydrated, and was passing frequent small green stools. The most conspicuous symptom was the regular projectile vomiting, the vomit containing much mucus but no obvious bile. The stomach appeared large under the abdominal wall, and gastric peristalsis was once observed. No pyloric tumour was felt.

An opaque meal, given on January 9, showed obvious obstruction to the emptying of the stomach, and barium was vomited as long as ten hours after the meal. Gastric lavage was therefore ordered twice daily, and the child given small feeds of a half-cream dried milk every two hours. One vomit showed traces of bile. The vomiting was much reduced by these measures. After twelve days the wash-outs were free of mucus and were reduced to once daily. The feeds were altered to four-hourly feeds.

On January 28 a second opaque meal was given which showed that food was leaving the stomach much more quickly than before. On February 5 a third meal was given, this time immediately after gastric lavage, and the diagnosis of duodenal obstruction was confirmed (see below).

Subsequent progress was slow but satisfactory. In order to keep the vomiting entirely in abeyance gastric lavage was still necessary every third day at the end of March. Gastric peristalsis was seen several times. Massage to the limbs and back was useful to get tissue assimilation restarted.

By April she was a good colour and very contented, and at the age of six months her weight was 12½ lb. (See postscript, p. 193.)

RADIOGRAPHIC EXAMINATIONS. (1) On January 9, 1935, at eight weeks of age, an opaque meal of 2½ ounces of fluid barium was given. The stomach was much enlarged and ovoid in shape. A suspicion of duodenal stasis was seen in the descending duodenum in the first film. At one hour very little food had passed into the intestine, the calibre of which seemed unduly small. At two hours the amount of food in the small intestine was still very slight. Barium was vomited ten hours after the meal.

(2) On January 28 the opaque meal was repeated. Food passed much more quickly than in the previous examination and at four hours practically all the small meal had left the stomach.

(3) On February 5, immediately after gastric lavage, a third opaque meal, consisting this time of 4¾ ounces of fluid barium, was given in an attempt to display duodenal stasis. Fig. 7, taken from a film in the oblique position on ingestion, shows considerable enlargement of the stomach. The duodenal cap is also enlarged to some extent, and the descending part of the duodenum is seen. Fig. 8, from a film taken in the prone position at about the same time, shows a large ovoid stomach, devoid of peristalsis, and covering the region of the duodenal cap. Lying

below the lower border of the stomach is seen the duodenum, somewhat enlarged and showing stasis. For the purpose of reproduction the outline of the duodenum in this figure has been artificially emphasized.

Discussion.

Symptoms.—In the duodenal ileus (arterio-mesenteric compression) of infancy the factors responsible for the production of obstructive symptoms are the degree of compression of the duodenum with which the child is born, the volume of the feeds given, and the amount of distension of the stomach. On these depend the time of the first appearance of the symptoms and the severity of the vomiting. The influence of the congenital anatomical fault is obvious, yet it is not necessarily paramount. This is well illustrated in case 2 above, where the refusal of food and vomiting were apparent from the date of birth, and yet medical treatment was sufficient to allow satisfactory progress to be made. The influence of the size of the feeds and the distension of the stomach is also seen in the duodenal ileus of later infancy and early childhood as has been pointed out elsewhere. In them refusal of food is often the chief symptom until the child reaches an age when it can be forced to take more than it wants, and then vomiting of the obstructive type develops. In case 3 it is probable that the small size of the breast feeds from the primiparous mother accounts for the vomiting being comparatively mild for the first three weeks of the child's life. It is when the factor of gastric distension comes into operation that vomiting becomes of the obstructive type, large, regular, projectile, and showing mucus.

The earliest symptoms therefore consist either of refusal of food or, where normal feeds are taken, of vomiting. After a feed the infant, although not apparently in actual pain, wriggles about as if in discomfort until relieved by vomiting. The stomach is seen much enlarged and standing out under the abdominal wall, but waves of gastric peristalsis are not easily nor frequently to be detected. Their rarity is due to the fact that during times of severe obstruction the stomach is in a state of 'paralytic' distension, just as in some cases of hypertrophic pyloric stenosis peristalsis may be in abeyance until the stomach has been washed out for a day or two.

The presence of mucus in the vomit is of importance. In a study of the gastric contents in wasted infants[17] it was pointed out many years ago that the presence of an excess of mucin was characteristic of hypertrophic pyloric stenosis, and it may now be put forward that in any case of chronic vomiting in an infant the persistence of mucus in the vomit indicates obstruction high in the alimentary tract. It is due to the associated chronic gastritis. The presence of bile in the vomit is not, contrary to what might be expected, a cardinal feature in duodenal ileus of the type here described. It has been recorded in the rare cases of gross megaduodenum associated with duodenal ileus, but in the group now under discussion it is little in evidence, and it is important to realize that this is so. In case 1 no bile was seen in the vomit while the infant was under observation; in case 2 traces of bile were seen in the first two gastric

wash-outs; and in case 3 the vomit was on one occasion seen to be slightly tinged with bile. In hypertrophic pyloric stenosis bile is practically never seen in the vomit or wash-out.

Constipation is not so marked a feature in duodenal ileus as in pyloric stenosis. If the bowels are disordered it is usually by diarrhoea, probably secondary to the gastritis. In case 3, when first coming under observation, there was evident infective enteritis.

Radiography.—Examination by means of an opaque meal before treatment has been instituted usually reveals a much distended stomach, ovoid in shape, with its pyloric end covering the duodenal cap. It also shows that the meal passes very slowly into the small intestine. Such a picture, although characteristic of duodenal ileus to those familiar with it, cannot be taken to prove more than that there is obstruction to the evacuation of the stomach and that the obstruction is incomplete.

If, however, the opaque meal be given directly after gastric lavage more positive evidence may be obtained. The stomach, although much enlarged, may be more normal in outline and the duodenal cap may be seen, especially in oblique views. Oblique and lateral views are nearly always necessary to expose the duodenal cap, because in postero-anterior views it is usually covered by the enlarged stomach. It is essential to see the cap at some period of the examination in order to demonstrate a normal pyloric canal with no increase in the pyloro-duodenal gap, thereby excluding even a minor degree of congenital pyloric stenosis. Lastly, although this cannot be guaranteed at any single examination, evidence of stasis in some part of the duodenum below the cap may be caught.

The use of an opaque meal, therefore, is of great value in diagnosis. It proves the presence of an obstruction to the evacuation of the stomach, and shows that the obstruction is incomplete and not situated at the pylorus. With careful technique and some perseverance it will also show evidence of duodenal stasis. On the other hand the actual emptying time of the stomach is more conveniently estimated by passing a tube into the stomach four hours after a meal than by radiographic examination. In case 3 barium was vomited as long as ten hours after the meal, and it is impracticable to submit a small infant to so many exposures of x-rays as might be necessary to determine the exact emptying time of the stomach.

In order to get the best and most immediate results by radiography two points should be kept in mind: first, the opaque meal should be given directly after the stomach has been thoroughly washed out; and secondly, the meal given should be considerably larger than the normal to allow for the enlargement of the stomach.

Diagnosis.—Where serious vomiting dates from birth (as in cases 1 and 2) the presence of obstruction is obvious, and the chief difficulty is to determine whether it is complete or incomplete. In a new-born baby who is keeping down only small quantities of food it may be

extraordinarily difficult to be sure if any milk is passing into the intestine. An opaque meal will, however, settle this matter at once.

Where, as in case 3, the initial vomiting is less urgent, the chief difficulty is to establish the presence of organic obstruction. Here a positive diagnosis may be reached by a consideration of the distension of the stomach, the discomfort after feeds, the occasional occurrence of visible gastric peristalsis, the forceful nature of the vomiting, and the presence of mucus in the vomit. These signs indicate the presence of obstruction to the evacuation of the contents of the stomach, and in the absence of positive signs of hypertrophic pyloric stenosis tend to incriminate the duodenum. The absence of obvious bile in the vomit must not be taken to exclude duodenal obstruction of an incomplete type. Radiographic examination by an opaque meal, especially if undertaken directly after gastric lavage, will confirm the presence of high obstruction and will exclude pyloric stenosis. It may also give positive evidence locating the obstruction to the duodenum.

In these young infants there is, of course, no great amount of time available for investigation, and it may therefore be urged that, when a diagnosis of incomplete non-pyloric obstruction has been reached, the correct line to take is to order gastric lavage every twelve hours for one or two days before considering opening the abdomen.

Course.—The progress of these cases must depend to some extent on the degree of unalterable compression of the duodenum with which they are born; but from the examples recorded here there appears to be a good chance that, if by lavage and careful dieting the tone of the stomach is maintained and severe distension prevented, compensatory hypertrophy of the gastric wall will enable the obstruction to be overcome. Where the congenital compression is too severe to allow of progress by such means, it may be supposed that gross megaduodenum may develop. Even when progress is being well maintained and symptoms are in complete abeyance a certain amount of obstruction from the congenital compression still remains. This is well seen in the skiagrams of case 2 (figs. 5 and 6) taken at five months of age, where the enlargement of the stomach, the hypertrophy of its walls and the hyperperistalsis indicate the persistence of some degree of obstruction in the absence of any symptoms. The persistence of visible gastric peristalsis is of the same significance.

Study of congenital duodenal ileus in later infancy and early childhood shows the same thing. Although vomiting may have occurred in the earliest weeks of life, giving rise to a suspicion of pyloric stenosis, in most cases the chief early symptom is refusal of food, and by this means vomiting is kept in abeyance and the evidence of any form of obstruction is masked. At about the age of eighteen months, when the child is getting a mixed solid and fluid diet and can be forced to take more than it wants, bouts of obstructive vomiting become common. In the intervals between the attacks both clinical and radiographic examination will show clearly the persistence of some degree of obstruction.

At somewhere between the ages of seven and ten years the symptoms appear to die down spontaneously, owing presumably in some way to the growth of the child. Their disappearance at these ages is much hastened by the administration of a dry diet with drinks two to three hours after meals.

It is possible that not all cases entirely lose their symptoms in adolescence, and it may be suspected that some of the examples of severe dilatation of the stomach seen at this age owe their origin to chronic duodenal ileus. One patient under our observation at the age of seventeen years for extremely severe gastric dilatation, developed acute duodenal ileus after laparotomy fifteen years later.

It may be of interest to mention that during childhood chronic duodenal ileus does not seem to predispose towards such a post-operative risk. Acute duodenal ileus seems almost unknown in children, and several of our cases in children have been through operations for removal of the tonsils or for appendicitis without any untoward symptoms.

Treatment.—The chief aim in treatment is to prevent gastric accumulation and distension, and for this gastric lavage is most effective. A weak alkaline solution may be used, for in spite of the criticisms by biochemists of the use of alkalis for this purpose the method seems harmless and has the advantage of removing the mucus in the stomach more effectively than normal saline solution. The lavage should at first be given twice daily and this should be kept up until the wash-outs remain free of mucus. Then the interval between the treatments may be lengthened to 24 hours, and later to 36 or 48 hours. Any return of copious or projected vomits, or any reappearance of mucus in the stomach, indicates the need for more frequent lavage for the time being. In any case it will probably be twelve weeks or more before lavage can be entirely discontinued.

The second indication for treatment is to give an easily digested feed at properly spaced intervals. If breast milk is not available, dilute evaporated milk, or a half-cream dried milk may be given. It is easy to estimate the emptying time of the stomach by passing a tube at four hours after a feed to find the amount of residue, remembering that with lavage the stomach soon empties more rapidly as the vomiting lessens. Probably it is best to try to get straight on to four-hourly feeds, but where the infant's condition is very frail half the amounts may be given every two hours.

It should be clearly understood that in the class of case described here the enlargement of the duodenum is not sufficient to make the performance of duodeno-jejunostomy a practicable operation. We have had no experience of the other type of case showing gross megaduodenum. Probably here operation is a necessity, and in rather older children duodeno-jejunostomy has been successfully performed. It is generally admitted that a gastro-jejunostomy is not a successful procedure for chronic duodenal ileus and our experience in two cases without megaduodenum in small children beyond the age of infancy confirms this.

Summary and conclusions.

1. Three cases of chronic duodenal ileus from arterio-mesenteric compression in new-born infants are described and the evidence on which the diagnosis is based is submitted.

2. The chief clinical features of the syndrome consist of the enlarged stomach (gastromegaly) causing protrusion of the upper abdomen and showing occasional visible peristalsis; and vomiting of the obstructive type, the vomits being large, projected and containing mucus. Alternatively, refusal of food may keep the vomiting in abeyance for the time being.

3. Radiographic examination will demonstrate the presence of obstruction in mild cases, and in the severe ones will distinguish between complete and incomplete obstruction. It easily excludes any form of pyloric obstruction and, especially in oblique views, may demonstrate duodenal stasis. The opaque meal should be given directly after gastric lavage and should be considerably larger than the normal for the age to allow for the enlargement of the stomach.

4. Medical treatment, chiefly by means of gastric lavage, is capable of restoring the tone of the distended stomach, so that satisfactory progress is possible in spite of the persistence of some degree of duodenal obstruction.

5. It is urged that where symptoms suggesting duodenal stenosis or atresia are found to arise from an incomplete duodenal obstruction, the possibility of duodenal ileus should be considered and a brief trial made of medical measures before submitting the infant to the extreme risk of an abdominal operation.

6. In the exceptional cases, described by other authors, in which gross megaduodenum is present, operation is probably essential; but in the type described here there is no possibility of the performance of duodeno-jejunostomy.

Our cordial thanks are due to Miss Frost, radiographer at the Paddington Green Children's Hospital, for the skiagrams of case 1, and to Dr. A. J. Wells-Beard, late resident medical officer at the Victoria Hospital for Children, for the skiagrams of figures 3 and 4. We also gratefully acknowledge our indebtedness to Mr. C. E. Shattock, Mr. Jennings Marshall, Dr. T. P. Lewis, and Dr. Hilda Brade-Birks.

POSTSCRIPT.

Case 3. – At the age of six months (weight, 12½ lb.) this baby developed difficulty in breathing with signs of bronchopneumonia and died in thirty-six hours. Death was found at autopsy to be due to diphtheria, membrane extending from the larynx into the lungs. The unfortunate fatality appeared unconnected with the condition of the digestive tract.

Autopsy revealed the stomach considerably enlarged, with hypertrophied wall: evidence of chronic gastritis was clear. The pyloric wall partook in the hypertrophy of the rest of the stomach. The pyloric canal was dilated and its rugae flatter than normal. The first part of the duodenum

was enlarged and appeared proportionate to the size of the stomach. Then followed an inch or two where the duodenum was smaller, if not reduced to its normal size. From thence onwards to the duodeno-jejunal flexure the duodenum was much enlarged, at least to twice its normal size, with some hypertrophy of its wall. Emerging from behind the root of the mesentery it resumed its normal size: this change was not absolutely abrupt, but was spread over about two inches of the gut. Although the site of the obstruction thus corresponded to the position of the mesenteric root, it could not be determined that that structure was actually compressing the gut; but on the other hand there were no bands or adhesions to account for the obstruction. Apart from the conditions mentioned the rest of the examination showed nothing of interest.

The autopsy, therefore, fully proved the presence of duodenal obstruction at about the level of the root of the mesentery, and we were satisfied that our diagnosis of arterio-mesenteric compression was confirmed. That the gut, on emerging from behind the root of the mesentery, resumed its normal size gradually rather than abruptly, is probably to be explained by the fact that the infant had been without urgent obstructive symptoms for many weeks before death. That, apart from the obvious effects of obstruction, it could not be made out that the mesenteric root was actually pressing on the gut is in line with what is found in adult cases post mortem. In them it is well recognized that the degree of compression cannot be judged by the anatomical disposition of the parts at autopsy, and that the severity of the obstruction is to be computed by the symptoms during life. In the present case the obstruction was at one time so severe as to cause the infant to vomit barium no less than ten hours after ingestion.

In the light of the autopsy our interpretation of the case perhaps needs modification in one minor matter. It is possible that the influence of the congenital anatomical factor was less, and that of the accessory factor of distension was greater, than we realized; and perhaps it was this, rather than underfeeding, which was responsible for the mildness of the obstructive symptoms in the first three weeks of life.

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THE EARLY ANAEMIA OF PREMATURE INFANTS:

the haemoglobin level of immature babies in the first half-year of life and the effect during the first three months of blood injections and iron therapy

BY

HELEN M. M. MACKAY, M.D.Lond., F.R.C.P.,

Physician for Diseases of Infants to the Mothers' Hospital, Clapton; Member of the Staff of the Medical Research Council.

An anaemic baby is more susceptible to infection than the normal infant[3, 7] and this is an important factor in the mortality rate of infants of subnormal birth weight. Lichtenstein[6], from his extensive work with premature babies, concluded that these infants regularly become anaemic in the first months of life although they are not anaemic at birth. The average haemoglobin level of thirty-six premature infants examined by him in the third month of life was about 40 per cent. (ranging between about 30 per cent. and 50 per cent.). He found that healthy full-term babies only exceptionally showed a drop to below 60 per cent. Many others have reached similar conclusions, though usually the number of their cases has been smaller; for example, Kunckel[4] found in twenty-one premature babies, whose birth weight averaged four pounds, a drop to an average figure of 46 per cent. It has been generally accepted that premature babies at this age drop to much lower levels than full-term babies although they all start extra-uterine life with high haemoglobin levels. The author's observations on premature babies brought to the Queen's Hospital for Children for advice on feeding or management did not contradict these views. It should be borne in mind that the normal full-time infant always shows a considerable drop in haemoglobin level after birth, the lowest level being reached at about two to three months of age. This is followed by a rise in the second three months of life and then, if, as so often happens, a sufficiency of iron is not available, a renewed fall.

Object of investigation and clinical material.

The investigations described in this paper were carried out at the Mothers' Hospital, a maternity hospital in the north-east of London. The babies were either newly-born in-patients, or were attending the hospital welfare centre. The investigation was concerned with the haemoglobin level

during the first twenty-six weeks of life of babies of low birth weight, attention being chiefly focussed on the extent of the drop from birth to about the end of the third month of life, and how an excessive drop might be minimized. The author was not here concerned with the nutritional anaemia due to iron deficiency, so common in the second half-year of life, although babies of low birth weight are particularly likely to develop nutritional anaemia in its severer forms, and in some babies the effects of iron deficiency begin to appear between three and six months of age. This is shown by the fact that iron medication begun by about two months of age will often augment the rise in haemoglobin level normally occurring after this initial fall, i.e., betweeen, say, three and six months of age[7].

Effect of intramuscular blood injections.—The estimations were made with a Haldane (Price-Jones) haemoglobinometer[8] from blood taken from a prick in the heel: ninety-one babies weighing less than six pounds at birth and fifty-nine babies of birth weight over six pounds were examined. The first set of investigations was planned to observe the effect of intramuscular blood injections. Human blood serum or citrated human blood, given intramuscularly or by transfusion, appears in many cases to check the excessive drop in haemoglobin and red cells occurring in familial icterus gravis neonatorum and the allied severe anaemia of the new-born, and it was hoped to discover

TABLE 1.

EFFECT OF TREATMENT ON THE EXTENT OF THE DROP IN HAEMOGLOBIN LEVEL AFTER BIRTH.

Birth weight and group.	Average Hb. level.		Lowest average Hb. level.	Age of infants with lowest average.
	At birth.	Eighth day.		
A. CITRATED BLOOD INJECTIONS.				
3, 4 and 5 lb. odd.				
Injected cases ...	142·4 (16)	125·3 (16)	73·0 (8)	10th week
Controls	145·6 (22)	125·4 (20)	74·4 (8)	14th ,,
6 lb. and upwards.				
Injected cases ...	136·6 (22)	124·1 (19)	76·4 (13)	14th ,,
Controls	141·8 (28)	128·3 (27)	74·3 (9)	14th ,,
All birth weights.				
Injected cases ...	139·1 (38)	124·6 (35)	75·1 (21)	14th ,,
Controls	143·5 (50)	127·0 (47)	74·4 (17)	14th ,,
B. IRON THERAPY, started before 45 days old.				
3, 4 and 5 lb. odd.				
Iron cases ...	145·1 (32)	—	74·7 (20)	14th ,,
Controls	—	—	74·0 (21)	14th ,,

NOTE: Figures in brackets indicate the number of cases in each group.

if blood injections would have a comparable effect in premature babies. Babies were therefore given on the first, second or third day of life an intramuscular injection of 15 c.c. of human blood with one c.c. of one per cent. citrate solution, the blood being taken usually from the mother but occasionally from the father. Haemoglobin estimations were made by the author on the first and the eighth day of life, and subsequently in the fourth, sixth, tenth, fourteenth, eighteenth, twenty-second, and twenty-sixth week, whenever possible. The results are shown in table 1. The lowest average haemoglobin value was reached in each weight group in the tenth or fourteenth week. Babies under six pounds at birth dropped to an average figure of 73 per cent., whereas their controls dropped to 74·4 per cent.; the corresponding figures for babies over six pounds at birth were 76·4 per cent. and 74·3 per cent., and for both sets combined 75·1 per cent. and 74·4 per cent. Taking all the cases together the difference between injected cases and controls was therefore less than one per cent., so it must be concluded that injections of blood, as here given, did not diminish the drop in haemoglobin level occurring in the first three months of life. Comparison of the haemoglobin levels in four pairs of twins, one of each pair having had the injection of blood, led to the same conclusion. Yet one surprising fact emerged, namely, that there was very little difference between the lowest level reached by the bigger babies and the smaller babies respectively.

Effect of iron medication.—In a search for some cause for this unexpected result, it seemed necessary to make sure that iron administration played no part in minimizing the drop in the small babies, since most of the babies who continued to attend were given iron before one-and-a-half months old. There seemed various reasons against the hypothesis that iron deficiency played any part in this early anaemia of premature infants[9], for, unlike the nutritional anaemia of later infancy, it is not a hypochromic anaemia, and moreover, investigations have shown that the iron store in the liver increases up to two months of age[2]. Since, however, several workers[1, 5] have claimed that iron, or iron in conjunction with some other medication, is beneficial in such cases, the question needed investigation.

Since a single blood injection was evidently without effect in this connection, this factor was ignored, and cases were analyzed on the basis of their iron medication. Table 1 shows a comparison beween the lowest haemoglobin level reached by babies given iron and ammonium citrate from under forty-five days old (usually $4\frac{1}{2}$–$6\frac{3}{4}$ grains daily) and a group of babies who received no iron during the period under consideration[2]. All these infants were under six pounds at birth. The average minimum haemoglobin level in both groups was again very close, namely, 74·7 per cent. and 74·0 per cent. in the fourteenth week; a difference of less than one per cent. Thus these figures negative any prophylactic influence of iron in this connection.

Extent of drop in haemoglobin level in babies of different birth weights.—It looked, therefore, as if an attempt was being made to prevent an excessive drop in haemoglobin level in babies whose drop was not excessive. In order to compare larger numbers, babies of similar birth weight were grouped together, irrespective of whether or not they received blood injections, or the age of starting iron treatment, since both these factors were without influence on the haemoglobin level in the first three months of life.

Table 2 shows the average haemoglobin level at birth, and the lowest average reached by babies of different birth weights. It will be seen that with one exception the lowest average figure reached by each group varies with the birth weight, the babies three to four pounds at birth drop lowest, those of eight pounds and upwards drop least, but nevertheless the difference is small, only about six per cent. between the lowest level reached by these two groups at opposite extremes of birth weight. It is true that the total drop from birth of the three pound babies is considerably more than that of the eight and nine pound babies, because they start higher; the tiny babies dropped 80·8 per cent. as compared with a drop of 59·2 per cent. in the eight and nine pounders, a difference of 21·6 per cent.

TABLE 2.

RELATION BETWEEN BIRTH WEIGHT, THE AVERAGE HAEMOGLOBIN LEVEL AT BIRTH, AND THE LOWEST HAEMOGLOBIN LEVEL REACHED IN THE FIRST FOUR MONTHS OF LIFE.

Birth weight.	Average Hb. level.	No. of cases.	Lowest Hb. level.	No. of cases.	Age of infants with lowest average.
3 lb. to 4 lb. ...	153·0	5	72·2	6	14th week
4 lb. to 5 lb. ...	148·7	12	73·3	12	10th ,,
5 lb. to 6 lb. ...	146·6	33	76·0	20	14th ,,
6 lb. to 7 lb. ...	142·1	32	74·0	8	14th ,,
7 lb. to 8 lb. ...	140·8	44	75·2	9	14th ,,
8 lb. and upwards	137·8	30	78·6	5	14th ,,

The average haemoglobin level at birth in babies of different birth weights.—The average haemoglobin level at birth is in inverse order to the birth weight; the babies weighing three to four pounds at birth averaged 153 per cent. on the first day of life, those of eight pounds and over, about 138 per cent. The author has already published figures for the average haemoglobin value at birth of babies weighing five pounds and over when born[9], and those now given (which incorporate the first set of figures) are for the most part lower. This is apparently due to the selection of cases; in the first series the babies were all rigidly selected as healthy and normal in every way, whereas in this second series, though no babies obviously ill were included, there were a proportion who were subnormal in vigour and general progress. Individual haemoglobin levels at birth showed very wide variation. In apparently

normal babies under six pounds at birth the maximum figure was 179 per cent. and minimum 105 per cent.; in babies over six pounds at birth maximum and minimum were 174 per cent. and 110 per cent. respectively.

The haemoglobin curve for babies under six pounds at birth.—The average haemoglobin levels during the first six months of life of babies of three to five pounds at birth and those of five to six pounds at birth

TABLE 3.

THE HAEMOGLOBIN LEVEL DURING THE FIRST SIX MONTHS OF LIFE OF BABIES WEIGHING FIVE POUNDS AND UNDER AT BIRTH.

(Figures on which chart is based.)

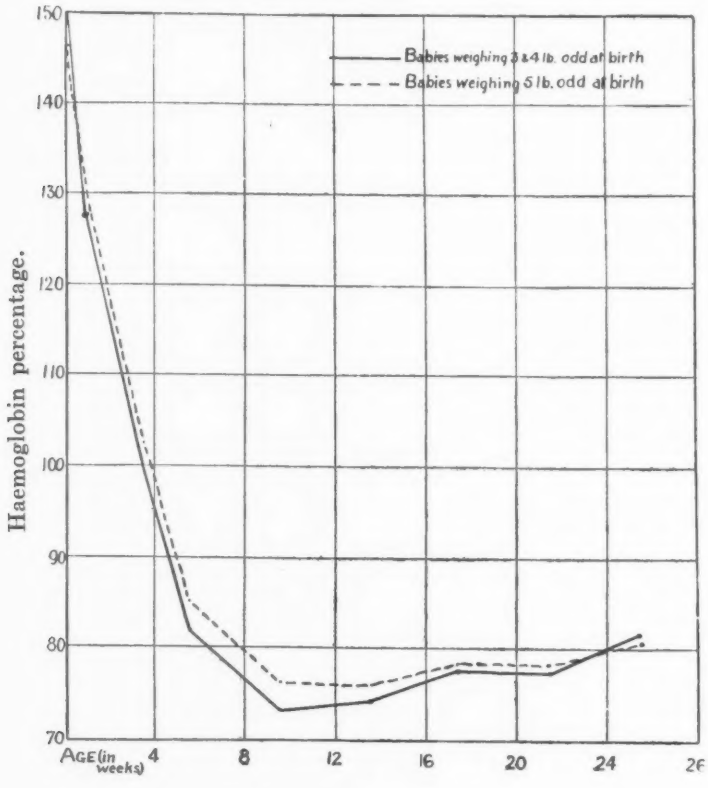
Age:	1st day	8th day	4th wk.	6th wk.	10th wk.	14th wk.	18th wk.	22nd wk.	26th wk.
Birth weight 3 and 4 lb. odd	149·9	127·9	100·1	82·1	73·4	74·4	77·8	77·3	81·7
No. of cases ...	17	23	21	20	19	14	13	4	12
Birth weight 5 lb. odd	146·6	130·0	102·7	85·1	76·3	76·0	78·5	78·3	80·8
No. of cases ...	33	46	25	30	22	20	24	15	14

are shown in the chart and in table 3. The smaller babies start higher, but from the eighth day until the twenty-second week are consistently slightly lower than the larger babies. At the end of the sixth month (twenty-sixth week) both groups averaged just over 80 per cent. in spite of the fact that iron medication in some cases is known to have been irregular. All babies were ordered iron from the fourteenth week of life, if they were not having it before.

Possible influence of general management and feeding.—After this digression regarding haemoglobin values at birth and the haemoglobin curve in immature babies, the factors which may have prevented the premature and immature babies in this series from showing any marked anaemia by the tenth or fourteenth week of life may be considered. There was nothing unusual in the type of feeding given to these children, unless it be that they were not given highly diluted feeds. Whenever possible they were given breast milk, feeding being started within a few hours of birth. The smaller premature babies and twins were given the milk of other mothers during the first weeks of life if no milk was available from the infant's own mother. If artificial feeding was employed, it was usually dried milk (half cream and later full cream), sugar and water, in the calorie concentration of 20 calories to each ounce. Whenever possible the calorie allowance reached 50 calories

per pound body weight by about one week old, sometimes before, and was subsequently further raised according to the appetite and rate of progress of the infants. Water was given between feeds as and when the baby would take it. Cod-liver oil emulsion and orange juice were started within the first few weeks of life. Thus these babies, on the whole, underwent no long period of underfeeding such as is frequently the lot of premature infants, nor were they given the very dilute feeds often associated with underfeeding. It is possible that both these factors played their part in the results here considered. Premature infants brought up to children's hospitals often after a period of much mismanagement give a different impression of the prognosis as regards life from that obtained in a maternity hospital, provided that the babies are adequately fed and kept warm from birth. Naturally the amount of illness suffered by these two groups also varies widely.

THE HAEMOGLOBIN LEVEL DURING THE FIRST SIX MONTHS OF LIFE OF BABIES WEIGHING FIVE POUNDS AND UNDER FIVE POUNDS AT BIRTH.



Haemoglobin levels in babies with pathological conditions.—May it be that it is primarily the general health and well-being of the infant which determines the extent of this early drop in haemoglobin level? On this point the present investigation does not provide sufficient material to reach any final conclusion, but several cases are suggestive. From the various tables

given in this paper six babies were excluded because they had definite pathological symptoms. The clinical records are as follows:—

M. S., birth weight 2 lb. 5 oz. Suffered from repeated cyanotic attacks and abdominal distension, necessitating underfeeding; poor gain in weight. Died at about ten weeks old. Haemoglobin in tenth week 35 per cent. (average in tenth week for babies three pounds odd at birth was 73·4 per cent.).

J. B., birth weight 2 lb. 6 oz. Suffered from oedema, abdominal distension and otorrhoea; poor gain in first ten weeks of life. Haemoglobin in tenth week 47 per cent. (average in tenth week for three-pound babies 73·4 per cent.). Good progress thereafter. Haemoglobin rose to 86 per cent. by six months old (with iron medication).

A. T., birth weight 3 lb. 2 oz. Suffered from cyanotic attacks. Haemoglobin in tenth week 58 per cent. (average in tenth week for three-pound babies, 73·4 per cent.).

J. T., birth weight 4 lb. 7 oz. Suffered from sclerema. Haemoglobin on the first day of life 115 per cent. Haemoglobin of twin on first day 170 per cent. (Average haemoglobin of babies four pounds odd at birth 148·7 per cent.)

D. J., birth weight 4 lb. 6 oz. Suffered from oedema. Lowest haemoglobin level reached is unknown, as estimations were not done at the requisite ages, but in the eighteenth week the haemoglobin was 69 per cent. (average for babies four pounds odd at birth 77 per cent.)

M. G., birth weight 5 lb. 14 oz. Suffered from oedema. Lowest haemoglobin level reached is unknown, as no estimations were made after the sixth week when it was 75 per cent. (average for babies weighing at birth five pounds odd was 85 per cent. at this age).

Thus every one of these six cases, excluded as having definitely pathological conditions, showed haemoglobin levels considerably below the average. Of four patients whose haemoglobin levels were available at the tenth or fourteenth week, three dropped to 35 per cent., 47 per cent. and 58 per cent. respectively. No other premature or immature child in the present series dropped below 63 per cent. It is true that the two babies who dropped below 50 per cent. were both under three pounds at birth (i.e., were more immature than any babies included in our series), nevertheless they both had in addition symptoms of severe pathological conditions.

Some babies were included although they could not be passed as absolutely normal. Five are noted as taking poorly during the first week of life or longer, so that there was considerable difficulty with the feeding; of these, three had haemoglobin levels well below the average. Three are noted as having ' shock ' or ' white asphyxia ' at birth, but making a rapid recovery. Of these, none showed especially low haemoglobin values, though one dropped more rapidly than usual. One baby suffered from abdominal distension in the early days and its drop was lower than average.

Discussion.

The case histories of the patients quoted above, showing that ten out of fifteen immature babies who had pathological symptoms, severe or slight, developed haemoglobin levels well below the average, at least suggest that it is some factor or factors associated with the general health which bring about the very low haemoglobin levels noted by so many authors in premature babies in the first three months of life. Such a suggestion, of course, does not elucidate the actual cause of the excessive drops. In the normal infant during the first two months of life—the period when the haemoglobin level is falling—it seems probable that two factors are acting: increased haemolysis and decreased red cell formation[9]. When, in the second quarter year of life, the haemoglobin is rising, there has already come about an augmentation in the rate of red cell production. Is an excessive drop in an immature baby usually due to excessive haemolysis, or to a delay in the age of augmentation of red cell formation to beyond the normal, or to a combination of these factors? And if these factors operate what is the mechanism of the changes? So far these questions are unsettled. Another theory has been put forward by Sanpaolesi[10] which is that hydraemia plays an important rôle. He found in twelve premature infants a loss in the total solids of the blood in the second month of life which reached its maximum in the third month, with a parallel decrease in red cells and haemoglobin. There was not, however, any alteration in the weight curves to indicate water retention. So far as the author is aware this work has not yet been confirmed. From Sanpaolesi's work presumably a loss of solid elements must be supposed rather than an increase of fluid in the third month of life or else a change in the relative amount of water in the circulation and in the tissues. If there is a loss from the body of solid elements of the blood without change in the blood volume, the low blood cell counts would still indicate that the total number of corpuscles in circulation in the body was subnormal. The observations recorded in this paper throw no light on these points, though it is interesting that the four babies excluded from the tables in this paper because they had suffered from oedema did show subnormal haemoglobin levels. There exists no definite knowledge at the present time of the cause of oedema in new born babies, though excessive cooling of the body appears to predispose to this condition.

Summary.

Observations were made at the Mothers' Hospital, London, on the haemoglobin level of 150 infants during the first half year of life. The main object in view was to obtain information regarding the fall in haemoglobin level during the first two to three months of babies of low birth weight. Of the babies examined, 39 were under five pounds in weight at birth, 52 were five to six pounds, and 59 were six pounds and upwards. Estimations were made with a Haldane (Price-Jones) haemoglobinometer on blood obtained

from a prick in the heel. When babies showing symptoms of definitely pathological conditions in the early days of life were excluded, it was found that the lowest average haemoglobin level reached in the first half year of life by the babies weighing three pounds odd at birth (72·2 per cent.) was only six per cent. lower than that of those weighing eight and nine pounds at birth (78·6 per cent.); the total drop of the three-pound group was, however, considerably greater than that of the eight and nine-pound group because they started life with a higher average haemoglobin level, thus these immature babies dropped 80·8 per cent. as compared with a drop of 59·2 per cent. in the big babies.

No influence on the extent of the drop in haemoglobin level in the first two to three months of life was observed as a result of giving an intramuscular injection of 15 c.c. of citrated human blood within the first three days of life, nor from the administration of iron and ammonium citrate by mouth.

Figures are given for the average haemoglobin level during the first six months of life of babies weighing at birth three and four pounds and five pounds respectively. Not one of these babies dropped below 63 per cent. The three and four pounders started with a higher haemoglobin level than the five pounders, but from the eighth day until the twenty-second were consistently slightly lower than the bigger babies. Babies showing symptoms of any severe pathological condition in the early weeks of life were excluded from these groups. It is suggested that premature and immature babies whose general health and progress have been satisfactory from birth do not usually show any severe anaemia during the first three months of life. The mechanism which brings about an excessive fall in haemoglobin remains unexplained—possibly excessive haemolysis, diminished red cell production and hydraemia may all play their part in varying degree.

The investigation involved the resident medical staff of the Mothers' Hospital, who gave all the citrated blood injections, in much extra work. The author's sincere thanks are due to all those medical officers who have held office during 1933 and 1934 for their generous co-operation, as well as to the nursing staff for their unvarying assistance. Her thanks are also due to Miss Lorel Goodfellow for her help in the analysis of the figures.

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BRITISH PAEDIATRIC ASSOCIATION.

PROCEEDINGS OF THE EIGHTH ANNUAL GENERAL MEETING.

The Eighth Annual General Meeting was held at the Slieve Donard Hotel, Newcastle, County Down, on Friday and Saturday, the 3rd and 4th May, 1935.

FIRST SESSION (MAY 3RD, 10 A.M.).

Business Proceedings : The President, Dr. Hugh Thursfield (London), was in the Chair, and there were present 45 members.

The Minutes of the last Meeting were read and approved.

The following Officers, Honorary, Corresponding and Ordinary Members were elected.

President : 1935-36, Professor A. E. Naish (Sheffield).

Secretary : Dr. A. G. Maitland-Jones (re-elected).

Treasurer : Dr. H. Morley Fletcher (re-elected).

Representative for Scotland : Dr. William Brown (Aberdeen) in place of Dr. G. B. Fleming.

Honorary Members : Dr. Eric Pritchard (Past President) and Professor T. G. Moorhead (Dublin).

Corresponding Members : Prof. K. D. Blackfan (U.S.A.), Prof. J. Brennemann (U.S.A.), Prof. Alan Brown (Canada), Prof. H. B. Cushing (Canada), Prof. I. Jundell (Sweden), Dr. C. L. Leipoldt (S. Africa), Prof. C. Marfan (France), Dr. E. M. Stephen (Australasia).

Ordinary Members : Dr. W. J. Pearson (London), Dr. C. B. Perry (Bristol), Dr. R. E. Steen (Dublin), Dr. W. C. Smallwood (Birmingham).

Next Meeting : The selection of the next place of Meeting was left to the Executive Committee.

The Treasurer's Report was received and adopted.

It was proposed by Dr. Morley Fletcher, and seconded by Dr. Alan Moncrieff, that a sum of ten guineas be sent to the funds of the Academic Assistance Council as a gesture of goodwill on the part of the British Paediatric Association. This was carried unanimously.

The President then outlined the policy decided upon with reference to the purchase of old paediatric books.

Communications :

1. DR. REGINALD LIGHTWOOD (London): 'Calcium infarction of the kidneys in infants.' Among 850 autopsies at the Hospital for Sick Children, Great Ormond Street, six infants, without any underlying renal disease, shewed heavy deposits of insoluble calcium salts in the renal tubles (calcium infarction). Their ages at death ranged from 5 to 11 months. Working backwards from this post-mortem finding,

an analysis of the clinical records was made. This showed certain features common to these cases. The symptoms of anorexia, constipation and failure to thrive occurred in all, obstinate vomiting in three. On examination the principle features were wasting and muscle hypotonia; the vomit might be slightly blood-stained. Sometimes the urine contained a little albumen, a few leucocytes and bacilli, but there was no response to orthodox treatment for pyelitis. The immediate cause of death was a terminal infection and pus was usually found in the middle ears. The blood urea became raised.

Pathologically, the calcium infarcts were recognizable to the naked eye as radial, whitish lines from the boundary zone towards the pyramids. On section the kidneys were gritty, and microscopically the mineral masses were seen in the collecting tubules, dilatation and distortion of the latter resulting. In one instance calcium was found deposited in a medium-sized artery in relation to the internal elastic lamina.

Neither clinical, pathological nor bio-chemical study has yet indicated the cause of the process. There was no evidence of parathyroid or other endocrine disturbance, the feeding could not be blamed and vitamin D preparations had not been given in excess.

2. Dr. F. J. Ford (Glasgow): 'Two cases of Schüller-Christian syndrome.' The histories and clinical observations on two children suffering from xanthomatosis were surveyed. In one case, a boy of $2\frac{11}{12}$ yr. began to have polydipsia and polyuria at $2\frac{4}{12}$ yr. He was admitted to hospital with consolidation of both lungs. Later it was found that he had defects in the skull bones, diabetes insipidus, infantilism (confirmed by radiological examination), transient Parkinsonian symptoms, enlarged spleen, and a blood cholesterol varying from 190 to 250 mgm. per cent. Since coming under observation, a year ago, the enlarged spleen, tremor, and some of the skull defects have disappeared. Diabetes insipidus remains unchanged. The spontaneous variation in severity of the disease was advanced as the most probable reason for any improvements noted, as the boy has had no treatment other than limitation of fat intake.

The second case was that of a boy of 9 years who had shown increasing adiposity for four years, following operation for appendicitis. He was found to have bilateral papilloedema which subsided in about a month, small skull defects, a flattened sella, and a blood cholesterol varying from 210 to 320 mgm. per cent. He was given thyroid and has not gained any more weight in the past four months.

3. Dr. E. Bellingham Smith (London): 'Myelomatosis in a baby.' In view of the uncertainty of the diagnosis the publication of details is not wished for by the author.

4. Dr. Eric Pritchard (London): 'The frequency of sub-scorbutic conditions in infancy.' He referred to the frequency of sub-scorbutic conditions in infants, who otherwise appeared to be healthy. Apart from the absence of ascorbic acid in the urine, or its reduction in amount, there was at present no available test for sub-scorbutic conditions, which was unfortunate, as they were often the precursors of serious developments. The prophylactic requirement of ascorbic acid for infants was about 15 mgm. daily. This quantity could be provided by about 300 c.c. of good breast milk, so that breast-fed infants usually got enough, but sometimes even breast milk contained little or no ascorbic acid, as was the case with a woman at present in The Infants Hospital, who had a baby suffering from a severe degree of cranio-tabes, which might be associated with the vitamin deficiency. The amount of ascorbic acid in cow's milk was usually about ten times less than that in breast milk. Pasteurized and dried milks, as well as practically all patent foods, contained no measurable amounts of ascorbic acid. Hence all artificially-fed infants should

receive supplementary supplies of vitamin C. The prophylactic requirement for an infant was afforded by 1 oz. of orange juice, or 3 oz. of tomato juice, or 60 oz. of grape juice. The curative dose for scurvy was about five times as great, hence the great value of being able to give vitamin C in the pure form.

5. Dr. Donald Paterson (London) and Dr. R. H. Bailey, introduced by Dr. Paterson: 'Preliminary notes on convalescent serum, vaccine, and skin tests in whooping cough.' During the past four years convalescent serum from cases of whooping cough has been given to children suffering from pertussis without good effect. In 95 contact cases, in which serum was given, 42 per cent. did not develop the disease, 32 per cent. had a mild attack and 26 per cent. had an unmodified attack. In a similar series of control cases in which no serum was given, 11 per cent. did not develop the disease, 20 per cent. had a mild attack and 69 per cent. had an unmodified attack. It may be said that convalescent serum is of considerable value as a temporary protection to contacts against pertussis. Marshall Findlay immunizing monkeys against pertussis with Sauer's vaccine demonstrated an intracutaneous skin test analogous to a Mantoux test, using Sauer's vaccine as an antigen. A considerable number of children were tested and all those having had whooping cough previously gave a positive test, suggesting that their skin had been sensitized by the pertussis antigen. Children who gave a negative skin test were then immunized with Sauer's vaccine and within three weeks developed a positive skin test. Children giving a negative skin test at the beginning of an attack of pertussis, gave a positive skin test in two to three weeks after the disease developed. The speakers believed that the skin test will be of considerable value in the early diagnosis of pertussis, and also in the detecting of those susceptible to whooping cough, and in determining the efficiency of vaccination against infection.

6. Dr. H. Stewart (Belfast): 'Enterococcal agglutinations in chorea.' In a paper published in the Ulster Medical Journal, October, 1934, Sir Thomas Houston drew attention to the enterococcus and its relation to rheumatism. He endeavoured to correlate the findings of other observers and suggested that all cocci isolated in rheumatic conditions might be enterococci infected with a phage. If the rheumatic origin of chorea is accepted it is reasonable to suppose that an agglutination of the blood serum from choreic cases to the organism responsible would be obtained. Of 32 cases of chorea so tested using the enterococcus as an antigen the following results were found:—

Number of cases positive to type A enterococcus		19.
Number of cases positive to type B	,,	10.
Number of negative cases		3.

Some positive cases were positive to types A and B. Twenty-six carefully selected control cases were also tested and all were negative, except one which gave a slight agglutination to type B. The results give definite support to the work quoted originally and open up a large field for speculation, particularly as to treatment with vaccine or serum. A number of cases have been treated by the enterococcal vaccine, but it is too soon to draw any conclusions. Vaccine therapy is certainly as good as any other remedy for the immediate treatment, but it has always been combined with rest in bed.

7. Dr. W. R. F. Collis (Dublin): 'Acute aseptic lymphocytic meningitis.' The patient, a girl aged 5½ years, was admitted to the National Children's Hospital, Dublin, with all the signs and symptoms of tuberculous meningitis (stupor, vomiting, fever, stiffness of the neck, Kernig's sign): all other systems of the body were normal including the ears. The C.S.F. on admission shewed an increase in globulin, chloride ·66 gm. per cent., cells 2,155 (98 per cent. monocytes). The child, however, made an uninterrupted recovery in two weeks, the C.S.F. returning to normal. At no time

were tubercle bacilli found in the C.S.F. and the Mantoux test was repeatedly negative (in a dilution of $\frac{1}{10}$ old tuberculin) even when the child had apparently completely recovered. At first the diagnosis of tuberculous meningitis was made, but later when the child recovered this appeared untenable. Dr. Collis found that text-books gave no help in elucidating the problem, but that a condition called acute aseptic meningitis, which had first been described in 1925 by Wallgren, now appeared to be recognized both in America and in the Continent as a definite disease syndrome, over 100 cases having been recorded in the literature. This recognized syndrome may be summarized as follows:—1. Acute onset of definite meningitic symptoms. C.S.F.: (a) Preponderance of lymphocytes; (b) Sterility of liquid; and (c) Chlorides usually normal. 2. Short duration of disease, benign and not followed by complications. 3. Absence of parameningitic conditions, e.g., otitis, sinusitis, trauma, etc., or of general infections, such as typhoid. 4. Absence of associated conditions such as mumps, herpes, encephalitis, etc.

8. Dr. D. W. Winnicott (London): 'Further notes on non-rheumatic pains.' He reported progress in regard to the diagnosis of children sent to his clinic with pains not truly rheumatic. For some years all cases sent by responsible people as possibly rheumatic or choreic have been kept under observation till school-leaving age, whatever the diagnosis made at the first interview. Of the last 459 cases a diagnosis of true rheumatism or chorea had proved correct in 40 per cent.; 48 per cent. had fallen into a wide group of psychological disorders labelled 'finding life difficult.' The remaining 12 per cent. have been found to have some physical disease other than rheumatic. The problem of non-rheumatic pains is, therefore, one which cannot be shelved by those in charge of rheumatism clinics, since it is as bad for those children who are 'finding life difficult' to be treated by compulsory rest as it is for rheumatic children to be forced to do drill. Of this comprehensive group 60 per cent. are normal or psychoneurotic and 40 per cent. psychotic (depressed, etc.) of the last 50 cases the sex incidence is as follows: of the 30 psychoneurotic cases, 16 girls and 14 boys; of the 20 psychotic: depressed cases, 13 girls, 3 boys; schizoid cases, 1 girl, 3 boys.

Second Session (May 3rd, 8.30 p.m.)

9. Dr. Hugh Ashby (Manchester) opened a discussion on 'The punishment of children.' Any punishment that is given by an adult, he said, should be prompt and calculated to the intelligence of the child. Punishment thoughtlessly and hapazardly applied will not act as a deterrent and too mild a punishment has no effect as this leads to the spoilt child who has only got to make a fuss and he gets all he wants. A simple practical threat, that a child knows can and will be carried out, is always effective. Punishment at boy's schools used to be too severe—this has now changed as masters have become more understanding and better teachers. The better the master the less punishment he has to administer. It is far better to reward good conduct than to punish bad conduct. This line of action has proved a great success even at an institution like Borstal. Any punishment that has to be administered must be distasteful to the boy and above all he must not be deprived of exercise. The old idea of making a boy write out so many lines should be given up and some form of exercise like drilling instead of playing games should be substituted. Corporal punishment should be reserved for very serious offences only.

He was followed by Dr. Robert Marshall (Belfast), and in the subsequent discussion the following took part:—Drs. K. D. Wilkinson (Birmingham), W. R. F. Collis (Dublin), D. W. Winnicott (London), A. Ogilvie (Newcastle), J. S. Y. Rogers (Dundee), and R. H. Bailey (London).

Third Session (May 4th, 10.30 a.m.)

10. Dr. W. S. Craig (Edinburgh) introduced by Prof. G. B. Fleming: 'Some remarks on the multiple puncture tuberculin skin test.' Attention was drawn to

the reliability, rapidity, and extreme simplicity of the method. The instrument and technique were described in detail in the *Arch. Dis. Childh.*, 1931, VI, 357. Experience with the test in large numbers of individuals over a period of five years indicated that it is as sensitive as the Mantoux method (using a 1 in 10 dilution of old tuberculin) and more reliable than the Pirquet method. During that time the multiple puncture test failed to give a reaction in six cases of established tuberculous infection. These were tested only a few days before death and in them all the Mantoux test (1 : 10) was equally unsuccessful. Reactions were obtained in 99 per cent. of over 1,000 adult city hospital patients and in all of 140 cases of tuberculous meningitis in children. Other points emphasized in connection with the test were:—(1) The undiluted O.T. employed remains potent indefinitely. (2) Sloughing does not occur even with the severest reactions. (3) The test is painless. (4) The test can be carried out in the matter of seconds and fifty individuals can be tested in twenty minutes.

11. Dr. C. W. Vining (Leeds): 'Remarks with reference to the chronicity of tuberculous bronchopneumonia.' The speaker fully appeciated the fact that small children frequently recovered from lung lesions due to tuberculosis, but he had not until recently believed that tuberculous bronchopneumonia was a form of the disease which had anything but a fatal termination nor had he thought it likely that a child would live more than a few months with such a condition. He mentioned three children under the age of five years who had lived one year, seventeen months, and three-and-a-half years respectively, the last child being still alive, and, apart from cough, free from symptoms and physical signs. Tubercle bacilli had been recovered from each case and the x-ray serial photographs were typical of tuberculous bronchopneumonia. In the case of the last child the x-ray films showed a gradual clearing of the lung fields leaving small local deposits of calcium.

12. Dr. W. T. W. Paxton (Glasgow) introduced by Prof. G. B. Fleming: 'The histology of icterus gravis.' The histological findings in five cases of icterus gravis and three of anaemia haemolytica neonatorum were summarized and illustrated by photo-micrographs. All cases of the former showed the presence of erythropoietic foci in the liver, and in two cases also in the spleen. In one case megakaryocytes were found in the liver. A variable degree of degeneration of the liver cells was present, and in some cases a fine periportal, and pericellular fibrosis. Iron deposition occurred in all cases in the liver and spleen, and less frequently in the kidneys and lymph glands. Leucopoiesis was more active than erythropoiesis in the bone marrow, although in both there was a variable shift to the left. Erythroblastosis was found to be more marked and more primitive in anaemia haemolytica neonatorum than in icterus gravis. Mention was made of a preliminary investigation into the effect on the red cells in icterus gravis, in normal infants and older children, of a haemolytic serum prepared by injecting human red corpuscles into a rabbit. The cells of the only case of icterus gravis examined were more susceptible to destruction by the lysin than the corpuscles either of normal infants with or without icterus neonatorum or of those of older children.

13. Prof. L. G. Parsons and Dr. W. C. Smallwood (Birmingham): 'A hitherto undescribed type of haemolytic (erythronoclastic) anaemia.' The patient was a male child, aged 7 years. He was first seen in August, 1934, with a profound anaemia. Blood count: R.B.C. 2·2 mills. per c.mm. Hb. 23 per cent. W.B.C. 7,200 per c.mm. Reticulocytes 6 per cent. Differential white cell count showed one per cent. of myelocytes and 5 normoblasts per 100 white cells. Red cells at this time and subsequently showed a very extreme degree of poikilocytosis with occasional sickle cell forms; some anisocytosis, punctate basophilia and microcytosis. M.D. 6·516 μ. Red cell fragility in saline showed increased resistance. Platelets were plentiful. The spleen was enlarged three to four finger breadths below the costal margin and was hard. Superficial lymph glands were slightly enlarged. There was no clinical icterus but cafe-au-lait skin pigmentation was present. Van den Bergh

reaction gave an indirect positive result with 0·8 units. The urine showed excess of urobilin and urobilinogen: lead was not present except after injection of parathormone. Blood W.R. negative. X-ray of bones showed rarefaction, especially well marked in the skull, which was thickened. Blood calcium 12·8 mgm. per cent. Calcium balance negative. Although believed to be of pure British stock, the boy's appearance was suggestive of some negroid admixture. Anthropological investigation did not confirm this. Treatment was first by intravenous blood transfusion and subsequently with iron and liver. After transfusion the anaemia gradually increased in spite of medicinal treatment. The essential characteristics of the blood picture remained unaltered. Attempts to increase the amount of red cell sickling by incubating moist preparations were unsuccessful and sickle cell anaemia was therefore excluded. The condition was thought to resemble most closely Cooley's erythroblastic anaemia but to differ from that condition in the late onset of symptoms, the extreme poikilocytosis of the red cells and the absence of the large pale irregularly staining red cells typical of Cooley's anaemia occurring in a child of apparently pure British stock.

14. Dr. W. Brown (Aberdeen): 'Congenital eventration of diaphragm.' A girl of $7\frac{1}{2}$, as an infant was cyanosed with rapid shallow breathing. On examination she showed dextrocardia and had pain in left lower thorax after large meals. The sternum was funnel-shaped with depressions at each side, especially on left. X-ray examinations (barium meal and enema) showed left diaphragm immobile and replaced by thin membrane reaching to level of sixth thoracic vertebra, and not domed but with an outline determined by gas-filled viscera underneath. The heart, trachea and mediastinum were displaced to right. The oesophagus was normal in length and direction but the stomach was turned upwards and over to the centre. Barium filled up the fundus and then spilled over to the pylorus. With the child lying on right side the meal readily reached the pylorus and now she is free from discomfort if she lies in this position, immediately after eating. The rest of the space under the diaphragm was occupied by a distended loop of distal transverse colon, the proximal part of which stretched from the right iliac region diagonally upwards across the abdomen. The liver border was below the right iliac crest. The small intestine was displaced to the left side of abdomen. Most accounts of this condition describe the splenic colon as occupying part of the space under the diaphragm but the splenic flexure is a fixed point and the dilated transverse colon was well above this in the case described.

15. Dr. Stanley Graham (Glasgow): 'Prematurity and neo-natal mortality.' Although the infantile mortality rate has been falling steadily, the neo-natal mortality has been practically uninfluenced by the modern welfare schemes and the first month of life remains as dangerous to the infant as it was at the end of the nineteenth century. In Scotland, prematurity is responsible for almost half the neonatal mortality and in a series of 921 cases of prematurity, two-thirds of the deaths in the neonatal period occurred in the first 48 hours of life (52·8 per cent. in first 24 hours, 13 per cent. in second 24 hours). It is unlikely that much can be done to lessen the incidence of prematurity but more prompt and skilled attention to the needs of the infant in the first fifteen minutes of life is required. A specially trained nurse should be detailed for this work. The provision of breast milk in the feeding of such infants is also of paramount importance The present mortality rate must be regarded as too high.